The Management of

)NCHIAL ASTHMA

A GUIDE TO TREATMENT

by

HERBERT G. J. HERXHEIMER

M D Frankfort, L R.C P Ed, L.R C.S Ed, L.R.F P S Glas

Research Assistant, University College Hospital Medical School, Honorary Senior Hospital Medical Officer, University College Hospital, London, formerly Professor of Medicine at the University of Berlin

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PREFACE

TWO MAIN reasons have induced me to write this book. One reason is my ever-growing interest in this disorder, which attracted my curiosity many years ago; since 1944 I have had the opportunity of seeing more asthma patients than before. Going into the details of aetiology and treatment showed me every day more questions to be answered, more problems to be solved. This process continues and in view of this I may be judged rash to write a book on treatment.

This leads to the second reason: why I have written this book now· there is such a mass of therapeutic suggestions—many sound, many useless—that the inexperienced cannot possibly find their way through this undergrowth. Even the common text books do not give much guidance, with one notable exception. We possess a number of effective therapeutic measures They are, however, useless, if applied without careful study of the individual case and detailed knowledge of the variation of drug action. This leaves the physician and the practitioner to his own resources which, more often than not, are adrenaline, ephedrine and breathing exercises All these may be used in a way which excludes success Our knowledge of treatment has made sufficient progress to give the practitioner better guidance; if it is not possible to cure asthma in most cases, the lot of the patient can be improved much more than is generally known. It is the attention to detail that matters here more than anything else. It seemed to me necessary to review all the means at our disposal in order that the practitioner could reconsider his previous attitude and decide whether to try something new, or something old by a new method. It is quite clear that such a review may be antiquated to-morrow, when new discoveries have been made. This risk is the greater because of our lack of knowledge of the aetiology, but I have decided to take it.

My sincere thanks are due to Prof. R. S Pilcher for enabling

me to carry out experimental investigations, to Dr. Andrew Morland and Mr. Ivor Lewis who permitted me to study many of their patients. I am also much indebted to Dr. R. Oddie and Dr. Andrew Herxheimer for their invaluable help in editing the text.

Hx.

November, 1951.

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INTRODUCTION

BRONCHIAL asthma is a disorder which differs in many respects from other internal disorders. Its symptoms present a different picture in every patient, and it is probably one of the most variable diseases known. Its course is unpredictable, and improvements and deteriorations follow one another irregularly. In many patients, if not in all, psychological factors have an influence. It is a common complaint, often disabling and sometimes fatal, and no effective cure is known. Yet in no other disorder have so many different remedies been described and acclaimed as highly successful year after year. The *index cumulativus medicus*, 1947, for instance, records papers on the treatment of asthma by x-ray diathermy, pneumoperitoneum, electric shock, insulin shock, radon, phenolized cocaine, ethylenedisulphonate, ethyl alcohol, sulphurated mineral water, scorpion venom, spleen extract, khellin, lutein, nikethamide, sex hormones, bilateral stellectomy and bilateral anaesthesia of the sympathetic ganglia. Other years have brought other suggestions of treatment, most of which have been found useful by their authors but have not gained any support. Their initial success was probably due to the psychological influences which must be expected in a psychosomatic disease. Similar conclusions can be [illegible]

treatment, bacterial vaccines (autogenous or stock)—all had the same effect and most of the patients derived benefit.

The situation of the general practitioner and the physician is, in these circumstances, embarrassing. They know that in this condition none of the recognized remedies can be relied upon and that if an improvement occurs the cause of this improvement often remains uncertain. The shrewd observer will see that the disease is influenced not by one or two but by many factors,

most of which cannot be identified, whilst in other diseases only one or two factors are causative and well defined. He might conclude that the complex interplay of many unknown factors would explain the continuous irregularity in the course of asthma, but would make rational treatment impossible.

The reaction of the doctor to this depends on his personality. The therapeutic optimist will use a remedy which he has once or twice seen to be "effective"; he will often be successful, because his honest optimism has a strong influence on the patient. The more critical practitioner will be diffident. He will try this or that, but regards the therapeutic result as accidental. Those who do not like to admit that there is no rational treatment prefer to regard the patient as a kind of *malade imaginaire* who only needs to forget his illness in order to be rid of it. In any case, most practitioners do not like asthmatic patients and the hospitals do not admit them if they can help it. If they must do so—and in the acute severe attack this is often the case—the discharge from hospital is arranged at an early date. All this is due to the conviction that lasting improvement cannot be achieved. Either spontaneous improvement, or the adjustment of the patient to his condition, seems all that can be hoped for.

This attitude is understandable, but unjustified. A disorder with many and complex causes may be difficult to treat, but [illegible]

is formidable and may seem to be beyond the powers of the practitioner. Yet it must be attempted if progress is to be made. We are in the fortunate position that the advent of the antihistamines and the study of allergic phenomena have opened new avenues of treatment. The discovery of ACTH and its effect is another promising achievement.

In these circumstances it seems desirable to review our present knowledge and experience of asthma therapy. I have made this attempt in order to give the reader a picture of the possible lines of treatment that are at present available and of the experience gained. It should enable him to judge whether

his past attitude is justified or whether it should be reconsidered. I have refrained from going into the questions of aetiology and diagnosis in more detail than the purpose of the book requires, but I have described the main avenues of treatment and given the technical details of those methods of treatment in which I have gained personal experience. Perhaps it will encourage the practitioner to treat his asthmatics according to these suggestions. I am convinced that they will often enable him to obtain considerable and lasting improvement and to prevent invalidism.

CHAPTER II

DEFINITION

BRONCHIAL asthma means a transient and usually repeated attack of breathlessness caused by bronchial obstruction. The obstruction may be due to spasm of the bronchial muscle, or to secretion into the bronchial lumen, or to oedema of the mucous membrane, or to any combination of these factors. Muscular spasm often is one of the factors, because in some cases the obstruction comes or goes so quickly that secretion or oedema could not have had time to develop or to disappear. If, for instance, in a case of induced pollen asthma, *iso*prenaline is inhaled, the obstruction begins to give way as early as 20 seconds after the end of an inhalation lasting 15 seconds, as I have often observed and spirometrically recorded (Fig 1). On the other hand, there are patients in whom secretion is the main cause of obstruction: some asthmatics who suffer from ample and viscous phlegm are not relieved by any substance which has [illegible]

oedema of the mucosa, is less easy to prove in man. In animals, Warren and Dixon (1948) have shown by their tracer method that antigen is taken up by the bronchial mucosa. In the fatal stages of anaphylactic shock antigen was chiefly localized in the submucous tissue, which was grossly oedematous. In man, the oedematous swelling of the nasal mucosa can easily be seen when an allergic stimulus is given; oedema of the bronchial mucosa is a frequent finding at the autopsy of patients who have died in an asthmatic attack (Urbach). It can be observed bronchoscopically during the attack (d'Abreu, 1940), but not in every case (Pasteur Vallery-Radot and his colleagues, 1950)

That the three factors may occur together is possible. The typical asthmatic attack with the sudden onset of obstruction

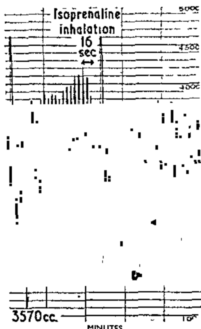


FIG 1 —EFFECT OF ISOPRENALINE INHALATION

An induced attack of pollen asthma is in progress The vital capacity has decreased to 2,800 cc. To stop the attack progressing, 2 per cent isoprenaline aerosol is inhaled for 16 seconds It can be seen that the tidal air excursions increase almost immediately after the end of the inhalation The vital capacity recorded 1 minute later is normal (3,570 cc) Its restoration to normal is entirely due to an increase of the reserve air which was reduced during the attack because of expiratory obstruction.
(By courtesy of the "Lancet")

which, at least partly, is of muscular origin is sufficient proof, for when the attack is over, a tough mucus is expectorated which in many patients is produced only during these attacks. Experiments by Dixon and Warren (1950) have shown that in certain stages of the attack the oedema, in others the muscular spasm is prominent. The question arises whether the three factors are perhaps in some way interdependent: whether hypersecretion in the asthmatic subject, once it is in action, causes muscular spasm, and *vice versa*. Little is known about such interaction, and it is difficult to investigate it experimentally because the same stimulus which causes hypersecretion may also touch off muscular spasm, without any interaction between the two. In one direction such an interaction may occur. If an asthmatic inhales a non-specific irritant gas, for instance small amounts of sulphur dioxide or nitrous oxide, the first reaction is usually cough, the sign of hypersecretion; tightness of the chest soon follows, but is not usually the first symptom. In some subjects who are prone to hypersecretion I have seen this happen also in attacks of grass-pollen asthma. The first sign of the developing attack was cough; dyspnoea was not noticeable at that time, but followed. In asthma induced by the inhalation of mixed mould extract the cough is often the primary symptom (Herxheimer, 1951). That bronchial spasm necessarily causes hypersecretion is less evident. On the contrary, there are a number of cases in which there is no

tuberculous lungs, all involve an inflamed mucosa and hypersecretion usually without obstruction. Some partial obstruction may be caused by accumulation of mucus and quickly

demonstrated by the sudden relief which follows the use of adrenaline or isoprenaline.

We may conclude that the bronchial obstruction called bronchial asthma may be caused, in some cases, by muscular spasm alone. In many, probably in most, cases it is caused by a combination of three factors: muscular spasm, hypersecretion and bronchial oedema which may be present in varying proportion. This may be called the "triple response of the bronchus" as parallel to the triple response of the skin of Lewis. The most essential part of this triple response is doubtless the bronchial spasm. It is possible that in some cases it may be caused indirectly by hypersecretion, but hypersecretion alone does not constitute bronchial asthma. Whether oedema without spasm occurs is not known.

If spasmodic contraction of the bronchial muscle is present, whether alone or together with hypersecretion and oedema of *the mucosa, the disorder is called bronchial asthma.*

CHAPTER III

DIAGNOSIS

The diagnosis of asthma rests more on the history than on the findings. Transient attacks of breathlessness unconnected with physical exertion or cough is suspect of asthma. The diagnosis is certain if the attacks are accompanied by an expiratory wheeze, or if they occur at characteristic times: at bedtime or on waking, or repeatedly during the night. Confirmation is given by their disappearance after the administration of adrenaline or isoprenaline, and their resolution with cough and expectoration of mucus.

These typical features may be accompanied by others less frequent: breathlessness on exertion, attacks of cough introducing the attacks of breathlessness, or constant mild shortness of breath with transitory increases in intensity. In some, cough may be the main or even the only symptom; it is then nocturnal or predominantly so. Breathlessness after exertion occurs mainly as an after-effect of the attack and is due to the concomitant acute emphysema which disappears only after some time.

The clinical signs in an asthmatic patient are few and of little importance compared with the history. There are expiratory, and often also inspiratory, rhonchi which are frequent during an attack and can often be heard at a distance. Between attacks they may be absent, but they can usually be elicited if the [illegible]

be present in a patient who has had asthma for many years if

there have been long periods of freedom. Other possible confirmatory evidence is eosinophilia and Charcot Leyden crystals or Curschmann's spirals if preserved from the previous attack. Skin testing for allergic sensitivity may reveal an allergic background. All these pieces of evidence are of value only if they are positive. If they are negative, asthma cannot be excluded.

If none of these tests offers confirmatory evidence a histamine test may be tried. If the patient is able to breathe a 3 per cent aerosol of histamine phosphate from a closed circuit for three minutes asthma is not present (Herxheimer, 1951). In asthmatics a severe attack usually develops after 12–60 seconds. The test must be interrupted at the first sign of a bronchial reaction and the inhalant changed to isoprenaline in order to abort the attack (Fig. 2). In some cases of asthmatic cough the diagnosis can be confirmed by the beneficial effect of treatment with ephedrine, adrenaline, or isoprenaline. Rossier (1944) and Wyss and Stocki (1949) have used this effect in an adrenaline and aleudrine test.

The details of diagnostic technique are not described as they are beyond the scope of this book.

Differential diagnosis.

The differential diagnosis does not present great difficulty. Nervous dyspnoea in excitable subjects sometimes shows itself in an asthma-like way. The subject desires for some reason to breathe more deeply than is possible and keeps his chest over-inflated; he experiences the inability of breathing in further and feels "breathless". This has nothing in common with asthma. Rhonchi are always absent, expiration is easy and there is never any serious dyspnoea. The picture of the attack may in some cases be so suggestive of true asthma that the histamine test is required.

Another possibility is that the dyspnoea is of cardiac origin. Cardiac asthma is a nocturnal complaint, as bronchial asthma often is. In the earlier stages cardiac asthma in the absence of pulmonary oedema may easily be mistaken for bronchial asthma. One main difference is that expiration is not especially difficult in cardiac asthma, and that wheezing is absent. The

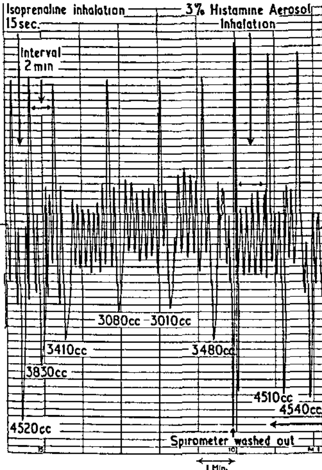


FIG 2.—HISTAMINE ATTACK

Male asthmatic [illegible]

presence of hypertension is not a reliable criterion, because hypertension may also occur in bronchial asthma. Vascular congestion of the lungs, however, present in cardiac asthma, never occurs in bronchial asthma. The circulation time, normal in the latter, is increased in cardiac asthma and can easily be determined in cases of doubt. There are a few cases of cardiac asthma in which bronchial spasm is present. Plotz (1947) has described a number of such cases. I suspect that bronchial spasm in these cases is secondary to the pulmonary congestion and not an originally asthmatic condition. The same occurs in some cases of right heart failure with pulmonary congestion, for instance in mitral stenosis. Such bronchial spasm usually recedes promptly when the heart failure improves. Recently Merkle and Wyss (1950) have stated that most cases of heart failure have bronchospasm, but this will require confirmation.

[illegible]

from the common bronchial asthma, only its aetiology differs. Treatment, however, may be greatly influenced by the eradication of the cause of the asthma. Into this group belong malignant tumours of the respiratory tract, tuberculous lesions and bronchiectasis. In some of these cases and in others, for instance obstruction by a foreign body or laryngeal obstruction from other causes, wheezing may arise from one point of obstruction only, where the air is forced through an extremely narrow passage. This does not justify the diagnosis of bronchial asthma because the obstruction is not caused by muscular spasm or by oedema. It is to such cases that the often-quoted dictum by Chevalier Jackson applies: "... not all is asthma that wheezes."

If emphysema is present, asthma must also be expected. Both disorders are very closely associated. Long-standing asthma leads sooner or later to emphysema. In other cases, emphysema develops during middle life or later for reasons not fully understood, and in these cases, bronchial spasm becomes associated with it from an early stage. I know of no case of clinically proved emphysema in which asthma was not present. It may be that it is absent in the very first stages, in which the diagnosis of

emphysema on clinical grounds is not yet possible. Later on, when the diagnosis of emphysema becomes possible, asthmatic obstruction can be expected with certainty. On this point I disagree with Whitfield, Arnott and Waterhouse (1950) who distinguish emphysema with and without bronchial spasm. They seem to think that the (temporary) absence of wheeze or rhonchi is evidence of the absence of bronchial spasm. It is difficult to understand why their patients without bronchial spasm all suffered from chronic cough and why they all had a considerably reduced vital capacity. As I have pointed out elsewhere (Herxheimer, 1949), the presence of emphysema alone cannot account for reduced vital capacity. A maximal muscular effort could still empty the lungs normally, if it did not encounter increased resistance, for instance from bronchial obstruction, skeletal changes or atrophy of the diaphragm. The last two are present in comparatively few cases; *in the vast majority it* is the bronchial spasm which causes obstruction; it reduces the vital capacity which now represents a lower percentage of the total lung capacity which is not altered in emphysema. It might be conceded that the degree of bronchial spasm varies in such patients, as it does in most chronic asthmatics, but there is not sufficient evidence for the continuous absence of bronchial spasm in emphysematous patients.

To sum up: the diagnosis of asthma rests in typical cases on the history and can usually be confirmed by signs, although this may be unnecessary. In atypical cases, such as asthmatic cough, the presence of asthmatic obstruction must be established. The same holds good for those cases in which asthma is not the leading but a secondary feature.

CHAPTER IV

TYPES OF ASTHMA

OF ALL classifications of asthma which have been put forward, none has been found satisfactory. This is natural enough as classification must satisfy the requirement of aetiology, symptomatology and morbid anatomy alike. This is impossible in a disease about which so little is known. One of the most popular classifications was suggested by Rackemann (1931). It divides the cases into extrinsic and intrinsic ones and has the obvious disadvantage that the intrinsic cases can be regarded as intrinsic only as long as their extrinsic nature is unknown

For the purposes of treatment a single classification will not suffice. We must use several systems of classification, as every type may need a different treatment.

We shall now consider various classifications and their merits.

The simple classification into severe, moderate and mild asthma is useful in determining the treatment; it will be shown later that the dosage of drugs varies for different degrees of asthmatic obstruction.

Acute asthma and chronic asthma

By acute asthma is meant the acute attack which develops [illegible]

mild form, with brief exacerbations superimposed upon it. The former occurs typically in children and adolescents, the latter in adults, although there are many exceptions to the rule Sometimes the acute form, present during childhood or adolescence, changes gradually into the chronic form: there are still violent acute attacks, but the intervals between them are no longer completely free. A mild wheeze persists continuously and becomes manifest on provocation. There are also some rare cases, in

which a constant mild wheeze is present for years without the patient being able to remember any violent attacks.

Status asthmaticus (asthmatic state) is a condition in which bronchial obstruction of great severity is maintained over a long period. It is a part of the picture of chronic asthma which in turn could be regarded as a mild asthmatic state. The difference between these *forms of asthma is of therapeutic importance*, as chronic asthma needs continuous treatment with drugs which have a long-lasting effect. The acute attacks require much stronger antagonists, the action of which however may be fleeting.

Classification according to special leading symptoms

Chronic asthma is sometimes only nocturnal or only diurnal. The patient is awakened once or several times during the night by a mild attack, but in the day does not experience any wheeze. In the rarer type night attacks are absent, and attacks occur on very mild exertion or even without any apparent cause during the day.

The bronchial obstruction may be caused mainly by secretion or mainly by spasm. In the latter case the wheeze is "dry" and cough and expectoration are absent, except after the end of an acute attack. In other cases the cough is the principal symptom, and without it no wheeze develops. Sometimes the wheeze is absent altogether and the cough is the only symptom Then [illegible]

for this distinction. It is one of the many types of asthma. The therapeutic importance of these various leading symptoms is clear, since nocturnal asthma requires different anti-asthmatic substances than diurnal asthma, and hypersecretion requires different treatment than dry asthma. It is possible that obstruction caused mainly by oedema should be distinguished from the other forms These may be the cases with continuous mild obstruction without any violent attacks. So far, a method is lacking to prove whether muscular spasm in these cases is an important factor

Aetiological classification

It is perhaps wrong to speak of aetiological classification. Important links in the aetiology of asthma are missing so that we know only comparatively little of the factors concerned. Nevertheless many attempts have been made to group the known factors: extrinsic and intrinsic asthma, atopic (heredi- [illegible]

[illegible]

factors but continuing after this factor has ceased to operate) and (v) asthma from unknown causes.

Such attempts at classification are bound to remain unsatisfactory. It is idle to contrast allergic asthma and non-allergic asthma, as our methods of detecting allergic factors are based on skin reactions and environmental investigations and are so unreliable that most of the so-called non-allergic cases may one day be proved to be allergic. Psychogenic asthma may have a purely psychological aetiology, but the evidence for this is not absolute. Urbach classes only 3 per cent of his cases as psychogenic, but even in these he admits that the psychological factor is the principal factor, not the only one.

There seem to be several ways in which the nervous system [illegible]

rabbits to the sound of a gong. It seems therefore justifiable to regard this type of asthma as being caused by a conditioned reflex (Rogerson, 1943). Another nervous or psychological influence is excitement Acute excitement may provoke an attack [illegible]

[illegible]

are not rare; damage to the nebulizer sometimes has a similar effect, and the patient often realizes the existence of a nervous factor. In such attacks a conditioning factor (the recollection of previous attacks) may perhaps play a part. On the other hand, the excitement of a game or of driving a car has been known to abort an attack. Acute anxiety probably plays some part in the further course of an attack. It is a common observation that attacks often start with very mild obstruction and then increase in severity. This increase might in some cases be attributed to the fear caused by the attack itself.

Excitement (worry or enjoyment) continuing over a long period also contributes to asthma, but here the mechanism may be different. A typical example is the little girl of 6–10 years who looks forward to going to a party. Sometimes the mother will volunteer the information that an attack has developed before the date of the party if the girl was told several days beforehand If she was told immediately before the party all went well. I have shown that in such cases hyperventilation with air may cause an acute attack whilst hyperventilation with carbon dioxide does not (Herxheimer, 1946) and I have ascribed the attack to the excess loss of carbon dioxide from the body tissues and its further consequences. It is well known that excitement may cause hyperventilation of considerable degree, and if it [illegible] dioxide may [illegible] the threefold inhalation of an inhalant allergen if present, and this overdosage of allergen alone may well be sufficient to cause an attack. A typical example of a case in which several factors may have acted together is that of a dust-sensitive boy of 14 years of age whose asthma had improved so much that he had been free from attacks for one year. One evening a fight developed with a younger brother because neither of them wanted to wipe the baby's nose. A general upheaval followed, which lasted more than an hour and involved a considerable "dust up", the parents being absent at the time. Later on, the boys were chastised by their parents; an attack developed the next morning. Probably the loss of carbon dioxide, the inhaled



FIG 3.—TRANSIENT BRONCHIAL OBSTRUCTION CAUSED BY PREVIOUS FORCED EXPIRATION

4–6 minutes.

dust, and the excitement were all causative factors, but we do not know their relative importance. Similar examples can be quoted from experience in the London "blitz". In a number of case-histories the first attack could be traced to the days of intense bomb damage in which the patient was involved. The first attack never started during the actual bombing, but a few days later. It may be assumed that a period of mental and physical strain and an environment full of dust had acted on the patient.

It is doubtful whether continuous worry acts through hyperventilation only. I have seen a woman patient whose mild chronic asthma became quite severe and could not be influenced by the usual treatment when she lost her job and was unemployed for 6 weeks. Immediately after she started in a new job the asthma reverted to its former very mild type. It is improbable that a loss of carbon dioxide should have continued to be effective over such a long period.

There are other influences, possibly of a nervous nature, which must be mentioned. In some asthmatics maximum expiration, which is strenuous and has to be carried out against some moderate obstruction, results in an immediate increase of the obstruction. If a continuous spirometric record is taken, the vital capacity initially appears normal, but the next full expiration, one minute later, is much more laboured and 300–900 millilitres less than before (Fig. 3). Further attempts may show a further decrease; after about 30 minutes' pause the original [illegible]

Another observation concerns the periodicity of attacks. In many patients with moderate chronic asthma mild attacks [illegible]

amount of antigen, a late effect may occur; but such a late attack occurs preferably in the evening of the same day or the next morning. Similar periodicities occur in vasomotor rhinitis. It

seems as if the conditions for the causation of an attack are particularly favourable at these times, so that they would convert latent asthma into an overt attack. There is no evidence that the contact with bedclothes or feather-beds is the reason for the vast majority of nocturnal attacks. The most likely explanation which occurs to me is that the same factors which cause the rhythmic changes in the 24-hour period, as for instance in temperature, urine secretion and sleep, are the cause and act possibly through the central nervous system. Other periodicities in asthma occur in connexion with menstruation [illegible]

[illegible]

and Schmidt-Ellmendorff, 1950). Naturally, endocrine influences have been suspected.

It is debatable whether irritation asthma is justified as a separate group. It is quite possible that irritation of the mucous membrane by non-specific agents, such as irritant gases and cold, may alone cause asthmatic obstruction; but the evidence for it is difficult to obtain as usually allergic factors become active very soon afterwards. The same holds for the so-called [illegible] the first attack, often

[illegible]

acute stage of the infection has passed and the temperature is returning to normal the first attack occurs. At this time bronchitis is still present, with much muco-purulent sputum, and although it is possible that the inflamed state of the mucosa is the main cause of the obstruction, now the bronchial muscle also becomes involved. Usually this asthma proves to be the forerunner of true allergic asthma. We must appreciate that such respiratory infections with consecutive acute bronchitis are very common, and that the development of an asthmatic attack as an immediate sequel is comparatively rare. In most of the subjects in whom it occurs, certain common allergies are soon [illegible]

[illegible]

allergy" or "infective asthma" exist in such a degree as some writers suggest.

A similar aetiological problem arises in emphysema. There is no case of emphysema in which there is not some degree of bronchial obstruction including muscular spasm, however small. This is quite definite: it can be proved by the beneficial action of ephedrine in typical emphysema, and also by the great susceptibility of emphysematous patients to histamine and

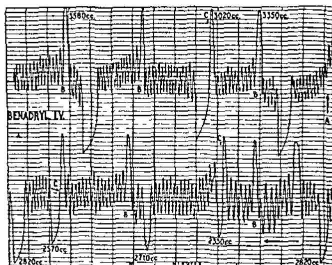
order to find out whether there was any allergic disposition in the subjects concerned In typical unselected asthmatics over 25 years of age the skin reaction was positive in 69 per cent. In patients under 25 years of age it was positive in 72 per cent if the asthma was severe and of long standing and in 58 per cent if it was mild. Separately grouped were typical cases of emphysema in which breathlessness on exertion had definitely been present before cough developed. The reaction was positive in 8 of 20 cases. In other patients with emphysema in whom chronic cough was the first symptom and had been present for many years, the breathlessness on exertion developing later, the skin reaction was positive in 15 of 50 cases. As the percentage found in normal subjects by Rimington and Maunsell (1950) is 4 per

been extended to bronchial sensitivity and not only to the skin.

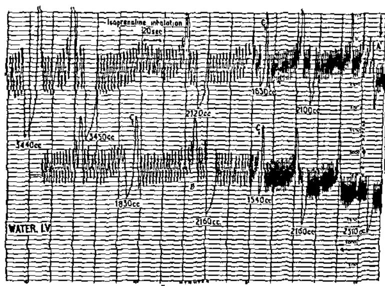
Two questions arise from these results: why does bronchial obstruction develop in emphysema? Is it necessary for an allergy to be present before it can develop? The fact that a positive

transient improvement can be achieved by many different methods, and therefore a large part of this improvement must be caused by psychological factors. Our next task is to find out whether methods of treatment exist which are successful apart from the associated psychological factors. Such a method must satisfy one of two criteria: either it must be possible to control it adequately or it must be successful in such a high proportion of cases that the successes necessarily include also those patients who are not liable to psychological influence. Two examples of methods which are undisputedly successful in almost all cases are the adrenaline-like substances, which can break up most attacks whatever their cause, and environmental treatment. There can be no doubt that in a monovalent allergic asthma, like grass-pollen asthma, the removal of the allergen leads to complete absence of asthma.

The other criterion is not easily available. If a substance or an action is expected to be of therapeutic value it would be desirable *to apply it in a certain number of patients and not to apply it in* an equal number of others who serve as "controls". This principle is equally valid for all other therapeutic measures. This method can only be applied under three conditions. (a) The approximately correct amount of substance must be known; otherwise it may happen that a quite ineffective therapeutic measure is compared with no measure at all (if, for instance, the dosage of adrenaline were unknown and the effect of too small an amount, say one minim, were explored with the help of controls, the result would probably lead one to conclude that adrenaline was ineffective). (b) The pathological disorder under treatment must be fairly constant and not liable to sudden variations; this latter condition is difficult to fulfil in asthma; only a minority of patients will conform to it. (c) Psychological effects of the measures taken should be excluded, as they would influence both the treated and the control (placebo) group alike. We have seen, and Graham, Wolf and Wolff (1950) have shown experimentally that *asthmatics can easily be influenced by such factors*; they may be of such strength in both groups as to blur the result of the measure under trial. If, for instance, 60 per cent of all patients in the experimental group and in the control group



3580cc.
3020cc.
3350cc.
BENADRYL I.V.
A
B
C
2570cc
2820cc
2710cc
2330cc
2820cc


Isoprenaline inhalation
20 sec
3440cc
3450cc
1830cc
2120cc
2160cc
1630cc
2100cc
1540cc
2160cc
2310cc
WATER. LV
A
B
C

[illegible]

are suggestible, and if it is assumed that the substance on trial will act positively in 50 per cent of the cases, there will be 75–85 per cent of positive results in the experimental group as compared with 60 per cent in the control group: an insignificant difference.

These conditions rule out as unreliable a large number of past therapeutic trials with asthmatics. They include the series of experiments in which the reports on symptoms by unselected asthmatic patients formed the basis of the result, whether with control groups or not, and also those in which the dosage was not varied widely. It is impossible to rely on the day-to-day changes in a patient's symptoms if they tend to change spontaneously. Negative findings under such conditions are just as valueless as positive ones; the pronouncement that "the dummies had it" is almost meaningless in asthma. The attempt must be made to use methods which are influenced neither by the spontaneous variations of asthma nor by psychological factors. Although the latter cannot be entirely eliminated, they can be reduced to a minimum. For this purpose an objective record of the respiration can be made to reflect the degree of bronchial obstruction. I have used the vital capacity as an indicator, and it has proved a simple, reliable method; the recording of the speed of the air-flow in expiration is more sensitive, but a very high degree of sensitivity also has disadvantages. If an asthmatic patient has a reduced but stable vital capacity, if he is able over long periods to record vital capacities which vary no more than in normal subjects, he can be subjected to therapeutic influences; these influences can be varied so that the patient does not know what effects to expect. Such precautions are necessary, as in very sensitive patients an attack may be brought on by apprehension alone. Apart from this possible error, the recording of the vital capacity is safe from psychological influences: I have never been able to increase or decrease it by suggesting that the condition of the patient had deteriorated. On the contrary, frequently the patient imagined such a change but the vital capacity remained unchanged (Fig. 4*a* and *b*). The method permits comparative measurements. If, for instance, a certain amount of isoprenaline aerosol is released into the closed spirometer circuit, most

patients will react in a way which depends on the degree of tolerance to the drug. Other aerosols, effective or not, can then be compared with the isoprenaline effect in the same patient.

If the asthmatic obstruction has reduced the vital capacity for some days, no anti-asthmatic substances will bring it back to normal at once; only partial increases are observed at one time and it usually takes several days to return to its normal value.

If substances are given orally, it is not always necessary to give inert substances as a control. If increasing doses of the same substance are given, the small and ineffective doses may serve as controls; with ephedrine, for instance, ½ grain and ¾ grain will often be found ineffective, whilst an increase in vital capacity may be found after 1 grain and still more after 1½ grains; larger doses in the same patient will not increase the effect but rather decrease it again because of the unpleasant side-effects (Herxheimer, 1946b). In some cases spirographic control may be omitted. These are patients who have a fairly constant [illegible] instance during [illegible] same drug [illegible] he doses to be compared are given in rotation at bedtime to the same patient over a period of one or two weeks. The method of recording the vital capacity repeatedly can also be used to record induced attacks of asthma. If minute amounts of an allergen aerosol are introduced into the breathing circuit, and the patient is sensitive to it, a very mild asthmatic attack develops. The development of the attack is so typical that it cannot be faked by psychological factors. In most cases no asthmatic obstruction can be traced in the first minute after inhalation. Only after 2–5 minutes the vital capacity begins to fall gradually, at first so little that the patient is unaware of it. Only after some time does the patient realize that he has an attack, which can then be aborted. Such induced attacks can be used to study the protective properties of certain substances and, of course, they are most valuable in controlling the process of hyposensitization.

All asthma therapy falls into one of three groups. (1) The elimination of the ultimate aetiological factor or factors so far as they are known. (2) The treatment of the symptoms with

effective antidotes. (3) The use of remedies the rationale of which is not known but which are believed to be effective.

Elimination of aetiological factors

Allergic sensitivity

It is generally assumed that the allergic reaction is due to the lack of sufficient circulating antibody which could neutralize the invading antigen. It is also assumed that it is possible to increase the circulating antibody by treatment; the treatment by hyposensitization is based on this assumption. Small amounts of the offending allergen are introduced into the body and if neither too small nor too large they may have the desired effect. If the amount is excessive it hypersensitizes (Herxheimer, 1951) instead of hyposensitizing. The difficulties lie in determining the correct dose and in choosing the route of administration. Injection methods have had some striking successes but the immediate observation of their action on the shock organ, the bronchi, is impossible. A general reaction after injection treatment is regarded as unfavourable, and therefore no reaction is aimed at. This lack of any objective external response to the progress of treatment is a great disadvantage. Its assessment must rely on the subjective reports of the patient. It is not surprising that Hurst in 1935 could not convince himself of the beneficial effect of such injection courses compared with saline solution injections. His scepticism is well justified. Improvement after hyposensitization means nothing unless the patient is exposed to the same allergic influences before and after the treatment. Such evidence is rarely presented, it is completely absent in the many cases of "co-seasonal" hyposensitization.

In the co-seasonal method which has been supported by Vaughan (1932) and Hansel (1941) very small doses of allergen are injected at intervals of 2 or 3 days. The dose remains the same or is raised slightly. Another method is the "rush" method described by Freeman in 1930. Here injections are given at very short intervals—from 20 minutes to 2 hours—in increasing doses. Some definite successes have been achieved with this method. Urbach and Gottlieb (1946) believe that they are due to de-allergization rather than hyposensitization. It is clear that the quick

increase in dosage greatly increases the danger of severe shock-like reactions and of hypersensitization. The method has therefore not found many supporters. All these injection methods seem capable of being successful; but there is no objective evidence to show which of them is likely to hyposensitize and under what conditions. As long as there is no reliable method of estimating the influence of injected allergen on the bronchi, neither dosage nor the very important interval between successive doses can be determined for each patient, and no benefit can be expected from such a procedure except by a happy accident.

Because of this difficulty, I have described (Herxheimer, 1951) a method of introducing the hyposensitizing amount of allergen as an aerosol into the bronchi, thus inducing minute attacks of asthma, which can be recorded by the spirograph. These small amounts increase the tolerance of the body (possibly by increasing the amount of circulating antibodies) and permit their gradual increase. By this method the increased resistance of the patient to a particular allergen can be proved directly and objectively, and the patient is exposed to it in the same way as in nature. If a patient at the beginning of the treatment responded with an attack to an amount A, of the allergen, and at its end is insensitive to A, the result can be regarded as very satisfactory. This measure of control cannot be achieved by the injection treatment, because it is started with a very small amount and progresses without any evidence of its effect except when overdosage occurs.

The main disadvantages of the aerosol method are the difficulty in finding the initial dose and the fact that the treatment is spread over a long period. Further study is required, but it appears that monovalent allergies can be successfully treated with it. In polyvalent allergies the course is often disturbed by the uncontrollable influence of external inhalants, and overdosage results; overdosage leads to hypersensitization which is a setback requiring a fresh start with very small doses. The [illegible] repetition of such setbacks may make [illegible] ses. In these and in [illegible] details of which are

described later (page 64), cannot be used because hypersensitization occurs too easily and may lead to a long period of even more severe asthma. The injection methods, of course, suffer from the same disadvantage.

A much simpler method is the elimination of all noxious allergens from the environment of the patient. This is sometimes very simple when single allergens are concerned, such as animal hairs or certain constituents of food or material handled. Sometimes hospitalization of the patient is sufficient, although here factors other than allergic ones may play a part. In many cases, however, especially when multiple allergies exist, their elimination is impossible.

Psychological and nervous factors

Aetiological treatment concerns all known contributory factors. Of these the psychological factor is of great importance. If a mental conflict is a contributory cause, it may be amenable to analytic treatment. If the social environment is the cause of the conflict, it may be possible to alter it. If general excitability is a contributory cause, sedation will be helpful.

The surgical interruption of the nervous supply has been used on asthmatics on a wide scale. Hesse (1933) reviewed the results of unilateral sympathectomy and vagotomy. Later, bilateral stellectomy (Leriche and Fontaine, 1939), bilateral resection of the pulmonary plexus (Gay and Rienhoff, 1942) [illegible] than most other therapeutic measures.

The successful result of such an operation may be due to the anaesthesia, or to associated psychological factors as well as to the operation itself. On the other hand, success cannot be expected in every case, because the nervous pathways, which are severed, may not be involved in the causation of the asthma. Nevertheless, there may be cases in which the nervous impulses play the primary causative part; if it were possible to pick out

these cases, the application of radical surgery would be justified.

Conditioned reflexes may play an important part in touching off an asthmatic attack. A man who has had an attack of asthma regularly every day when entering the crowded underground train on his way home from the office, will eventually get his attack regularly even if the underground train is empty and well ventilated. The story of the asthmatic patient who was sensitive to roses and went into an attack when shown an artificial rose has been mentioned earlier. These mechanisms might be attacked therapeutically by the same method which Pavlov has used experimentally.

Local irritability

Local irritability of the bronchi is another contributory factor. It can be observed that a patient's asthma flares up when he comes into contact with particles which have an irritant action. A schoolboy who handles sulphur dioxide in the chemical laboratory is a typical example; tobacco smoke is another, although in some cases this may have an allergic action. The action of an irritant produces characteristic sequence which contrasts sharply with the patient's usual attack. The first symptom is an irritation cough and the attack follows after a short interval. It is possible that non-specific inflammation of the bronchial mucosa acts in the same way. No method of influencing this irritability has been described unless the eradication of inflammatory foci is regarded as such.

Biochemical factors

The loss of an excess amount of carbon dioxide by hyper- [illegible]

acts as a contributory factor only if carbon dioxide is lost in excess. It is possible that the tendency of some patients to develop asthma after every meal has a similar background, namely the loss of hydrochloric acid into the stomach. Another possibly biochemically induced attack is the "early

morning wheeze", which is seen in the great majority of chronic asthmatics. This is a mild attack which occurs in the early hours of the morning, usually between 4 a.m. and 6 a.m. and which is very difficult to prevent. In nocturnal asthma one usually succeeds in suppressing the attacks by antihistamines given before bedtime, but this early morning attack is often not influenced even if the dose is much increased. As at this time of night the sleep becomes lighter, it is possible that carbon dioxide [illegible]

known, whereas hyperventilation can be diminished by explaining its effect to the patient or by the administration of sedatives.

Symptomatic treatment

Symptomatic treatment would be very satisfactory if it were possible to suppress all the symptoms all the time. The patient would be free from symptoms although the ultimate cause would remain untouched. A similar situation exists in the diabetic whose disease is well controlled by insulin. Unfortunately we are far from this ideal. Asthmatic obstruction is caused by muscular spasm and oedema of the mucosa, with or without hypersecretion. There are a number of substances which counter one or more of these factors. Adrenaline and its relative, isoprenaline, act primarily on the muscular spasm. This can be seen from the speed with which it acts. From the moment it has made contact with the mucous membrane only 20–40 seconds pass until its relieving action becomes evident (Fig. 1). No oedema or secretion [illegible]

effects of adrenaline do not appear together since it takes less time for a muscle to relax than for fluid to be removed from oedematous tissue. The mechanism of its action is unknown, but it is certain that it acts on bronchial obstruction whether it is caused by allergens or by histamine, acetylcholine or by what may be regarded as a nervous impulse. It is the most powerful

of all substances concerned, but its action is fleeting. After it has been absorbed its effect may last a few hours and often less. It is quite able to break up even violent attacks, but not to protect against them or against their recurrence for any longer period. It is not known whether adrenaline and its relatives directly influence bronchial secretion.

There are other substances the action of which persists longer. These are ephedrine and its relatives and the antihistamines. The beneficial influence of ephedrine in asthma has long been recognized. Although its action lasts much longer than that of adrenaline and isoprenaline, it is less powerful. It requires almost an hour after injection to become effective. Because of this delay and because of its relative weakness it is quite unsuitable for use in acute attacks. In mild chronic asthma and especially in the mild obstruction accompanying emphysema it is very effective. Its central stimulant effect increases its usefulness during the day, whereas at bedtime this factor will be a contra-indication. Tolerance develops easily, more easily than to adrenaline and isoprenaline.

The beneficial influence of the antihistamines in asthma is not yet generally recognized. After an initial enthusiastic reception based mainly on their effects on hay-fever and perennial rhinitis, and the uncritical evaluation of subjective reports from asthma patients, it was realized that beneficial effects in bronchial asthma were much rarer than expected. Some doubted that they occurred at all, and others thought that such effects were due [illegible] recently, however, experienced observers have produced evidence which does not support this attitude. Rubitsky and his col- [illegible] (1949), Ogden, Derbes and Cullick (1950), Gaillard (1950), and Finke (1950) report definite improvement after oral administration. Segal (1950) stresses their anti-asthmatic effect when given

intravenously. Feinberg, Malkiel and Feinberg (1950) think that they have a very beneficial action in the asthmatic cough of children and the cough preceding asthmatic attacks, but they stress that in other forms of asthma their effect is less than that of the sympathicommetic amines. I have shown (1949b) that mild pollen-induced asthmatic attacks can be prevented by antihistamines given orally; their effect is limited as that of ephedrine to the mild chronic forms of asthma and their sedative side-effect makes them especially suitable for administration at bedtime. Experimentally, Schild *et al* (1951) have shown that bronchial spasm caused in an isolated human bronchus by an antigen can be counteracted by an antihistamine in high concentration.

It seems therefore that these results discourage both undue enthusiasm and scepticism. It is certain that the antihistamines [illegible] to the mucous membrane. In bronchial asthma, smooth muscle is also involved, and the innervation is much more complex; apart from the autonomic innervation of mucosa and bronchial muscles the autonomic and cortical influences on the respiratory movements come into play The action of antihistamines in asthma is thus modified by many more factors than in allergic rhinitis.

Unfortunately there is little experimental evidence on the mechanisms of action of ephedrine and the antihistamines. Gaddum (1938) has advanced the theory that ephedrine acts by preventing the destruction of adrenaline by amine oxidase. This assumption would be supported if ephedrine were shown to have no effect on isolated [illegible] understand why ephedrine takes so much longer to act than adrenaline. Almost an hour is necessary, although this period does not seem to be required by absorption in the digestive tract. I have given the substance in enteric-coated form and

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It seems therefore that these results discourage both undue enthusiasm and scepticism It is certain that the antihistamines have some anti-asthmatic effect, and it remains to be seen under what conditions this effect can be utilized. We cannot expect the same effect as in allergic rhinitis, where the disorder is confined to the mucous membrane In bronchial asthma, smooth muscle is also involved, and the innervation is much more complex; apart from the autonomic innervation of mucosa and bronchial muscles the autonomic and cortical influences on the respiratory movements come into play The action of antihistamines in asthma is thus modified by many more factors than in allergic rhinitis.

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found that the effect was delayed by several hours. If ephedrine is absorbed, as other substances are, in 15–20 minutes, its enhancing action on adrenaline present in the tissues ought to appear at that time and not half an hour later.

This long latent period between administration and clinical effect is also seen in the action of the antihistamines. This fact must not be overlooked, especially as a delay of 10–20 minutes also occurs after intravenous injection of antihistamines. One *might suspect that both counteract an obstructing factor which* requires time to subside. Oedema of the mucosa is such a factor. If we, for one moment, assume that ephedrine and the antihistamines act mainly on the oedema, it would explain the delay in their action; this delay in their effect is pronounced, while with adrenaline and isoprenaline the effect is immediate. This difference might explain why neither antihistamines nor ephedrine can abolish acute or violent asthmatic obstruction, the sudden onset of which suggests a strong spasmodic element. Only in a few cases is it possible to distinguish the oedematous and the spasmodic factor in a case of obstruction. A possible example of such a case is given in Fig. 4*a*, page 20. Here intravenous Benadryl given to a chronic asthmatic decreases the chronic obstruction, as can be seen from the considerably increased vital capacity. *If, however, the obstruction is made worse by* [illegible] does.

If the antihistamines act mainly on oedema, it might also explain why their effect varies so much in different patients: we may assume that the proportion of oedema in the causation of bronchial obstruction also varies from patient to patient. Finally [illegible] This is, at present, no more than an assumption, for which evidence must be sought. If it is correct, it does not mean that the antihistamines have no direct effect on the bronchial muscle. In fact, from the experiments of Schild and his colleagues (1951)

with the isolated human bronchus it appears possible that they have. It is also possible that their effect on the mucosa has an indirect influence on the muscle.

The actual mechanism of action of ephedrine and the antihistamines on the mucosa or bronchial muscle is unknown. We know now for certain that in the causation of human asthma histamine is involved (Hawkins, Mongar and Schild, 1951a), and it might be assumed that the beneficial effect of the antihistamines is at least partly caused by their histamine antagonism. If histamine were to be regarded as the main cause of the attack, the sympathicomimetic amines must be regarded also as antihistamines. It is, however, doubtful whether histamine is the only factor involved. There may be other factors of equal or greater importance, for instance acetylcholine. It must not be forgotten that antihistamines also have a considerable anti-acetylcholine action (Schild, 1947) New pharmacological methods will be required to study these problems. Unless the changes in the bronchi can be observed in their natural state, with nervous and vascular supply intact, our knowledge will remain incomplete.

[illegible]

valuable because it rarely has side-effects. Very little is known [illegible]

[illegible]

chronic states, whereas aminophylline will be valuable in both forms This rather general rule must be modified to suit individual cases. A case in which hypersecretion is prominent will need an antihistamine with special antisecretory properties, or atropine. A case with viscous secretion will need iodide to loosen it and to promote its absorption (Gordonoff, 1938) and to promote expectoration When cough is prominent and is

degree of clinical improvement. Curry *et al.* (1950) and Herschfus, Levinson and Segal (1950) found that ACTH did not protect against induced histamine or methacholine asthma. As in animals it has been shown that neither sensitization nor anaphylactic shock is prevented by cortisone, one ought to conclude that cortisone does not prevent formation of antibodies or their union with the antigen; nor does it counteract histamine or acetylcholine acting independently. In spite of all this, it has a very definite anti-asthmatic action in many cases —possibly in most cases if one assumes that in some of the reported failures the dosage may have been too low. The claimed percentages of 70–80 per cent successes may not seem especially high in a disorder like asthma, but they can be regarded as genuine because of the severe and chronic type of illness treated and because of the regular relapse after discontinuation. We possess in ACTH and cortisone, substances which *are doubtless a great asset, but in the experimental* evidence they appear useless in asthma. Probably some of the early experimental results will be shown to be erroneous. It is clear that we have to wait for further investigations of this fascinating problem.

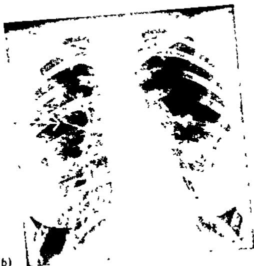
Other methods of treatment

Calcium treatment has been suggested on the ground that it decreases the excitability of the autonomic nervous system and the capillary sensitivity. Although its intravenous application often has a satisfactory result in some forms of urticaria and serum sickness, its effect in asthma is uncertain.

Sedation is a very important part of symptomatic treatment in asthma. It aims at depressing the general excitability of the asthmatic subject, which is assumed to be greater than in normal subjects. It may act in several ways, for instance by depressing *hyperventilation. It should be used in all cases in which* a psychological exciting factor is prominent. In acute cases and in the asthmatic state general anaesthesia has been used with reported *good effects.*

It must be admitted that both aetiological and symptomatic methods of treating asthma are unsatisfactory. In many cases





... month in 33-year-old female ... illness ...

... later these shadows have almost disappeared ... degree and was started with a short fever of unknown degree and was followed by a long-lasting improvement of the asthma



(c)

they do not remove the disorder and we must often be grateful when we see the worst symptoms disappear. In these circumstances it is necessary to see whether experience or chance observations offer any other possibilities. There are some observations which point the way to further progress. In some cases long remissions occur after pyrexia. After other decisive physical or psychological events—an abdominal operation or a great psychological shock—the asthma may disappear. I have also observed that sometimes after a pneumonia has healed, the asthma often disappears for an unusually long interval, often for many months. These pneumonias usually start with a temperature between 102°–104° which lasts for only 12–48 hours, and is often not noticed by the patient. Local symptoms (pleural pain) may be absent, and auscultatory signs are rare. Radiological appearances on the first or second day are typical but subside quickly, usually within one week (Fig 5 *a–c*) The shadows are never intense, and the process does not migrate to other parts of the lungs. The illness may occur several times in the same patient, at intervals of many months or years. It has some points in common with Löffler's syndrome, but as the infiltrations are never intense and do not migrate, and as a beneficial influence of Löffler's syndrome on the course of asthma has not been described, I hesitate to suggest that there is any connexion. Jaundice has also been described as beneficial to asthma, and recently Rosen and Levy (1950) and Kadlubowski (1950) have reported 5 cases and 1 case respectively These observations show that there are conditions under which the asthma may disappear, and often more completely than can be achieved by any treatment

In some cases treatment has been based on such observations. The fever treatment, usually with *Bacillus coli* vaccine (Klewitz, 1934) given intravenously in increasing dosage, has found some support. I have seen some successes, but as hospitalization is required for the treatment, it is, of course, possible that some of the successes are due to this Feinberg (1944) has induced artificial fever by diathermy. Other methods of shock treatment which have been tried are insulin shock and electric convulsion therapy.

X-ray irradiation has been recommended by a number of authors with different methods (Klewitz, 1934; Maytum and Leddy, 1939; Kaplan and Reubenfeld, 1943; Hull, Balyeat and Chout, 1944). Ultra-violet treatment has also been recommended (Miley, Seidel and Christensen, 1943) and success reported in the usual 80 per cent of the cases.

I have little doubt that injection treatment with non-specific substances or, as they are sometimes called, meta-specific substances, comes into the same category. Peptone, protein substances, autogenous blood stock bacterial vaccines, sulphur-in-oil and many other substances have been used, but it is certain that none of these methods led to lasting improvement. Usually one or several observers issue a more or less enthusiastic report which is, however, rarely confirmed. In most cases later authors report unfavourably and the remedy joins the great number of those which give good results only in the hands of enthusiastic or uncritical observers.

In spite of the scepticism with which these remedies must be judged, I am not convinced that they are all useless apart from their psychological effect which they share with many other methods of treatment. The percentage of success in those few methods which can be objectively controlled is, perhaps, little higher; it is possible that among the successes of "irrational" treatment reported by enthusiastic observers are hidden some "real" successes: one hopes that methods can be found which permit their repetition under controlled conditions. The long remissions of asthma after acute febrile respiratory infections are too numerous to be regarded as accidental. Further observations in this direction are required before any conclusions can be drawn.

CHAPTER VI

TECHNIQUE OF TREATMENT

General observations on drug dosage in bronchial asthma

In bronchial asthma drug dosage is governed by rules differing from those which apply to other diseases. Whatever the cause of asthmatic obstruction, it seems very likely that one or more substances (for instance histamine or acetylcholine or their precursors) produced in the bronchi are the immediate causative agents. This explanation would fit the observation that attacks of greater severity require a larger dose of antidote for their suppression. Whatever the correct explanation, it is certain that the dosage required in asthma varies enormously. It varies from patient to patient and from attack to attack, and it is not rare for one patient to require ten times more of one particular drug than another. This means that in every patient the dosage of whatever substance is to be given must be tried out individually. It means further that a therapeutically ineffective dose must be assumed to be too small unless it has toxic side-effects. It also means that in the same patient the dosage must be changed if the severity of the attack changes, so that day-to-day variations may be required. In some cases it is necessary to teach the patient how to adapt the dosage to his changing requirements.

As drugs may have to be given over long periods, the question of tolerance must be considered In my experience tolerance may develop to any drug in any patient. The danger of developing tolerance is greater with some drugs than with others, and there are patients who will not develop tolerance at all. It is not known how dosage and frequency of medication influence its development; with ephedrine I have observed that tolerance occurs more quickly if the intervals between the single doses are short (Herxheim- [illegible]
to other drugs. [illegible]
possible, and a [illegible]

previous one has ceased to act. It may seem unnecessary to emphasize this, but the habit of giving three daily doses of any medicine or tablet is so firmly established that I have often seen drugs known to act for 12–14 hours given in three daily doses. If signs of tolerance develop, the substance in question should be omitted and temporarily replaced by another. After some time it can be given again, but this should be done with less frequent daily doses than before. Alternatively, the substance should be given only for a period of a few days, and this should be followed by an interval of similar duration.

Sympathicomimetic amines

Adrenaline and isoprenaline

Adrenaline.—For a long time adrenaline has been regarded as the only effective means of checking an acute asthmatic attack. This is no longer correct, since isoprenaline (*iso*propyl*nor*adrenaline—known also as Aleudrine, Neoepinine and by other trade names) has a similar action. Both very quickly relieve bronchial obstruction in asthma. As this response is noticed within less than one minute, it is unlikely to be due to decongestion of mucous surfaces or lessening of secretion, both of which would take longer to occur, and the main response must be due to relaxation of bronchial muscle. An essential difference between the two substances is that isoprenaline does not possess the pressor action of adrenaline and that it directly stimulates respiration in man (Fig. 1). Moreover, the action of isoprenaline in asthmatics is stronger, weight for weight (Gay and Long, 1949). If tolerance to one substance has been acquired, the other substance still retains its effect.

The principle "the more severe the attack the more antidote must be given" also applies to adrenaline and isoprenaline. It is this principle which is often not followed in practice. Experience also shows that as an attack develops gradually, the most favourable time for counteraction is in its beginning. If the correct amount is given, the attack is cut off, at least for some time. If too little is given, another dose w[illegible] be required after a short interval. Unfortunately such [illegible] given at

TABLE I

SYMPATHICOMIMETIC AMINES

$(OH)_2C_6H_3$—CHOH—CH_2—NH_2	*Nor*adrenaline (Arterenol)
$(OH)_2C_6H_3$—CHOH—CH_2—NH—$CH(CH_3)_2$	Isoprenaline (*Iso*propyl*nor*adrenaline)
$(OH)_2C_6H_3$—CHOH—CH_2—$NHCH_3$	Adrenaline
C_6H_5—CHOH—$CHCH_3$—$NHCH_3$	Ephedrine
C_6H_5—CHOH—$CHCH_3$—NH_2	Propadrine
C_6H_5—CHOH—$CHCH_3$—$N(CH_3)_2$	Methylephedrine (Meteph)
C_6H_5—CH_2—$CHCH_3$—NH_2	Benzedrine (Amphetamine)
OHC_6H_4—CH_2—$CHCH_3$—NH_2	Paredrine

intervals of 15 minutes or longer have little effect. The reasons for this are not clear, but I have often seen that many repeated doses of 5 minims of adrenaline had no satisfactory effect, although the total amount if given at once gave complete relief. It looks as if repeated small doses counteract each other to a certain extent, and thus the impression of adrenaline-fastness is created, which in reality does not exist in these cases. The practitioner, in deciding the first dose to give, should be aware that too small an amount may be a serious mistake, and that asthmatics, in the absence of vascular complications, tolerate large amounts of adrenaline-like substances extremely well. In cases with hypersecretion in whom the smaller bronchi are filled with viscous mucus the dilator effect of adrenaline is insufficient to produce expectoration; the expected relief does not occur and adrenaline fastness is often suspected. In such cases the mucus must first be removed (*see* page 57).

Adrenaline can be given by subcutaneous, intramuscular or intravenous injection, or as an aerosol. For injection the hydrochloride or tartrate in 1:1,000 solution is used. The substance slows down its own absorption by its constricting action on the local blood vessels. It can be slowed down further by giving the adrenaline in oil or in another vehicle which delays absorption. In most cases quick action is required and it is therefore advisable to give the amount decided upon in several simultaneous injections in order to increase the rate of absorption; massage of the site of injection may have a similar effect. In order to avoid overdosage Hurst (1943) has recommended the "minim a minute" method; the injection needle is left in position and every minute 1 minim is injected until relief occurs. The only objection to this method is that in many cases the total dose is too small. If for instance, a patient requires 20 minims for relief, this amount would only be reached in 19 minutes. By that time the initial minims given would have lost their main effect; moreover, the attack may meanwhile have increased in intensity. The method may be useful in patients whose reaction to adrenaline is quite unknown, or who are unlikely to require more than a total of 10 minims. In all other cases it is advisable to give 2 or 3 minims a minute if the 1-minim method does not give substantial relief after 5 minutes. In a violent attack I prefer to give, in the absence of cardiovascular disease, 20 minims at once, unless it is known that the patient has had greater amounts in previous attacks. If the amount of 20 minims does not give substantial relief, this dosage is repeated at 5-minute intervals until relief is obtained. Acute emergencies may require higher doses. In recommending high dosage I am guided by the experience that more harm is usually done by too small than by too great a dosage of adrenaline. The relieving effect of the initial dose can be prolonged by giving a second dose of slowly absorbed adrenaline.

When judging the result of an injection, the psychological effect should be kept in mind. In many patients the beginning of an attack creates anxiety and fear, liable to increase its severity. The first feeling of relief removes this factor and acts as a valuable support to the genuine adrenaline effect.

The pressor effect of adrenaline has often prevented its use in the treatment of hypertensives. I think that the danger has been exaggerated; but as the pressor effect is absent with isoprenaline, this substance is preferable.

Intravenous adrenaline does not offer special advantages; its dosage is difficult to determine and the effect is fleeting.

Combinations of adrenaline with pituitrin (Asthmolysin) have no particular advantage. Adrenaline can be given as an aerosol, usually in 1 per cent solution. It can also be used in a 10 per cent solution:

Adrenaline	1·0
Chlorbutol .	0·09
Sodium bisulphite .	0·01
2N HCl . .	2·8 cc.
Sterile distilled water to	100·0 millilitres

(Larsen and Nielsen, 1937)

In my experience tolerance to adrenaline inhalation develops quickly. Combinations of adrenaline aerosol with other substances will be dealt with under aerosol combinations (*see* page 62).

Isoprenaline.—This substance (*iso*propyl*nor*adrenaline) first described by Konzett in 1940 and widely tried in Europe and the United States of America since the end of World War II, has proved most useful in bronchial asthma (Verzár and Voegtli, 1947; Segal and Beakey, 1947; Herxheimer, 1948a, Gay and Long, 1949). Its growing popularity is reflected in the fact that in Great Britain five different brands are available; it does not possess the pressor effect of adrenaline and its great practical advantage is that it is very effective when given sublingually.

The substance is the *iso*propyl derivative of *nor*adrenaline, the activity of which in asthma is at present under investigation. *Nor*adrenaline, unlike adrenaline, has no methyl group in its NH_2 and occurs in the human body together with adrenaline. In the animal experiment isoprenaline is much more effective against bronchial spasm than adrenaline In man it can be given

Adrenaline can be given by subcutaneous, intramuscular or intravenous injection, or as an aerosol. For injection the hydrochloride or tartrate in 1:1,000 solution is used. The substance slows down its own absorption by its constricting action on the local blood vessels. It can be slowed down further by giving the adrenaline in oil or in another vehicle which delays absorption. In most cases quick action is required and it is therefore advisable to give the amount decided upon in several simultaneous injections in order to increase the rate of absorption; massage of the site of injection may have a similar effect. In order to avoid overdosage Hurst (1943) has recommended the "minim a minute" method; the injection needle is left in position and every minute 1 minim is injected until relief occurs. The only objection to this method is that in many cases the total dose is too small. If for instance, a patient requires 20 minims for relief, this amount would only be reached in 19 minutes. By that time the initial minims given would have lost their main effect; moreover, the attack may meanwhile have increased in intensity. The method may be useful in patients whose reaction to adrenaline is quite unknown, or who are unlikely to require more than a total of 10 minims. In all other cases it is advisable to give 2 or 3 minims a minute if the 1-minim method does not give substantial relief after 5 minutes. In a violent attack I prefer to give, in the absence of cardiovascular disease, 20 minims at once, unless it is known that the patient has had greater amounts in previous attacks. If the amount of 20 minims does not give substantial relief, this dosage is repeated at 5-minute intervals until relief is obtained. Acute emergencies may require higher doses In recommending high dosage I am guided by the experience that more harm is usually done by too small than by too great a dosage of adrenaline. The relieving effect of the initial dose can be prolonged by giving a second dose of slowly absorbed adrenaline.

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[illegible]

have no particular advantage. Adrenaline can be given as an aerosol, usually in 1 per cent solution. It can also be used in a 10 per cent solution:

Adrenaline . .	1·0
Chlorbutol . .	0·05
Sodium bisulphite .	0·1
2N HCl . . .	2·5 c.c.
Sterile distilled water to	10·0 millilitres

(Larsen and Nielsen, [illegible])

In my experience tolerance to adrenaline inhalation develops quickly. Combinations of adrenaline aerosol with other substances will be dealt with under aerosol combinations (see page 62).

Isoprenaline.—This substance (isopropylnoradrenaline) first described by Konzett in 1940) and widely tried in Europe and the United States of America since the end of World War II, has proved most useful in bronchial asthma ([illegible] and Voegtli, 1947; Segal and Beakey, [illegible]; Herxheimer, [illegible]; Gay and Long, 1949). Its growing popularity is reflected in the fact that in Great Britain five different brands are available; it does not possess the pressor effect of adrenaline and its great practical advantage is that it is very effective when given sublingually.

The substance is the isopropyl derivative of noradrenaline, the activity of which in asthma is at present under investigation. Noradrenaline, unlike adrenaline, has no methyl group in its NH_2 and occurs in the human body together with adrenaline. In animal experiment isoprenaline is much more effective against bronchial spasm than adrenaline. In man it can be given

M.B.A.—4

subcutaneously, intravenously, orally, sublingually and *by* aerosol. Only the last two methods are useful in practice. Parenteral use is unnecessary and oral administration uncertain. Sublingually *the tablets should be allowed to disintegrate rather* than be sucked. If they are sucked, the saliva would be swallowed and the substance transferred to the stomach, where it is often destroyed. The sublingual dosage lies between 5 and 60 milligrams. It must be varied according to individual tolerance and to the severity of the attack. A useful method is to instruct the patient to take ½–1 whole tablet (10 or 20 milligrams) under the tongue and to wait from 3 to 4 minutes for the effect. If there is no satisfactory relief, another tablet should be added and so forth until sufficient relief is felt. It is essential that all the tablets should be held in the mouth simultaneously in order to increase the concentration of the substance in the saliva. It is [illegible]

adrenaline at intervals of 15–30 minutes. There need be no fear of overdosage as at the first sign of side symptoms the remaining tablets can be removed from the mouth. Palpitations and tachycardia frequently occur, but they are transient and harmless, *and the patient should be warned to expect them.* Angina- [illegible]

irritation and small ulcers of the bronchial mucosa, sublingual administration should be replaced by aerosol inhalation. The amounts which are effective by inhalation are much smaller, usually less than 1 milligram. The aerosol can be made from a 1–3 per cent solution. The 1 per cent solution is the standard concentration, and the more concentrated solution should be reserved for those patients who are by nature tolerant to the substance. It has been suggested that the 0·5 per cent solution should be used as the standard concentration. *I find that* the 1 per cent solution is more useful; the purpose of the inhalation is to suppress the attack as quickly as possible. The longer the

longer the inhalation lasts, the more voluntary hyperventilation with loss of excess carbon dioxide will occur, thus favouring bronchial obstruction. Any one of these reasons would justify the use of the stronger solution, the only disadvantage of which is that harmless and transient side symptoms may occur more readily.

Whether a patient should use sublingual tablets or the aerosol must be decided individually. Side symptoms are probably less common with the aerosol, as it acts locally before systemic effects occur. For patients who need isoprenaline several times daily, inhalation is often preferable, whilst patients who need it on rare occasions are better off with a tablet in their pocket than with the nebulizer.

The great practical advantage of isoprenaline is that the patient need not wait until the doctor arrives and gives the injection; this delay often permits the attack to grow in severity, because of the unavoidable anxiety connected with it. The advantage is especially great with children who soon learn that they can rely on it and lose their apprehension.

If one compares the effect of sublingual tablets with that of adrenaline injection, one will find that about 5 minims of adrenaline are roughly equivalent to 15 milligrams of isoprenaline. If the aerosols are compared, there is no doubt that the 1 per cent isoprenaline is more effective than the 1 per cent adrenaline aerosol, although exact assays in the human subject have not yet been attempted. It appears from this that sublingual administration is wasteful, as probably only a fraction of the amount dissolved in the saliva is actually absorbed.

Oral and aerosol administration, if repeated too frequently, will lead to tolerance The interval between inhalations should be at least 2 hours, that between sublingual administrations, 4 hours. Some patients become so dependent on the inhalation that they inhale every ½ hour for fear an attack may develop. This habit should be strongly resisted. Galgiani *et al* (1939) have reported damage to the mucous membrane caused by

subcutaneously, intravenously, orally, sublingually and by aerosol. Only the last two methods are useful in practice. Parenteral use is unnecessary and oral administration uncertain. Sublingually the tablets should be allowed to disintegrate rather than be sucked. If they are sucked, the saliva would be swallowed and the substance transferred to the stomach, where it is often destroyed. The sublingual dosage lies between 5 and 60 milligrams. It must be varied according to individual tolerance and to the severity of the attack. A useful method is to instruct the patient to take ½–1 whole tablet (10 or 20 milligrams) under the tongue and to wait from 3 to 4 minutes for the effect. If there is no satisfactory relief, another tablet should be added and so forth until sufficient relief is felt. It is essential that all the tablets should be held in the mouth simultaneously in order to increase the concentration of the substance in the saliva. It is [illegible]

adrenaline at intervals of 15–30 minutes. There need be no fear of overdosage as at the first sign of side symptoms the remaining tablets can be removed from the mouth. Palpitations and tachycardia frequently occur, but they are transient and harmless, *and the patient should be warned to expect them.* Angina-like attacks have been described but I have not observed any so far. In some cases, usually in children, nausea and vomiting occur, and sublingual administration is then undesirable. In these cases and in those few in which isoprenaline tablets cause irritation and small ulcers of the bronchial mucosa, sublingual administration should be replaced by aerosol inhalation. The *amounts which are effective by inhalation are much smaller,* usually less than 1 milligram. The aerosol can be made from a 1–3 per cent solution. The 1 per cent solution is the standard concentration, and the more concentrated solution should be reserved for those patients who are by nature tolerant to the substance. It has been suggested that the 0 5 per cent solution should be used as the standard concentration. I find that the *1 per cent solution is more useful; the purpose* of the inhalation o suppress the attack as quickly as possible. The longer the

of adrenaline an increased formation of histamine appears to take place (Halpern and Cruchaud, 1947; Bain, 1951). There is also experimental evidence that resistance to adrenaline developed in dogs if it was given by repeated intravenous injections (Vigran and Essex, 1950). This problem urgently requires experimental investigation.

Ephedrine

This drug has been used in asthma for many years, and the most detailed description of its action is still that given by Chen and Schmidt (1930). Ephedrine is of use only in mild chronic asthma. It never relieves acute attacks, because it takes a long time to become effective (usually 50 minutes) and because it is not powerful enough. In mild continuous bronchial spasm it often acts like a charm. The patient's breathing becomes easier and if there is retention of phlegm he is able to expectorate. The action lasts 6–8 hours, and its central stimulant effect makes it unsuitable for use at bedtime in adults, unless it is combined with a potent sedative. In children the stimulating effect is often not strong enough to disturb sleep. In some children, and in a very few adults, its effect is sedative instead of stimulating.

As mentioned before, almost an hour elapses after ingestion before it becomes effective. This property which it shares with many antihistamines is of practical importance. In a considerable number of patients the period after waking is the most trying time, during which the cough, or the wheeze, becomes severe. If ephedrine is given at the beginning of this period its action will miss the time when it is most needed. In such cases the patient should be instructed to take the drug one hour or longer before getting up. If necessary he must be awakened for this purpose.

In the bronchial spasm of emphysema ephedrine is still one of the best remedies known. The mild chronic spasm occurring in this disorder seems to respond more promptly to ephedrine than does ordinary bronchial asthma.

Ephedrine is thus one of the few substances suitable for treatment during the day. It is effective only if given in its optimal dosage. This dosage is different in every patient and therefore

repeated inhalation of adrenaline in animals. These findings have not been confirmed. In later experiments similar damage after isoprenaline inhalation has not been found (Herxheimer and Short, 1949). Isoprenaline in combinations with other substances will be dealt with in a later chapter.

Hamburger, Milliez and Halpern (1946) have advanced the view that the usual doses of adrenaline and isoprenaline are too large. They recommend much smaller amounts, for instance a 0 1 per cent isoprenaline aerosol instead of the 1 per cent solution. They had found in animal experiments that if a dose of isoprenaline preceded a dose of acetylcholine the bronchoconstrictor effect of the latter was increased, and they *believe* therefore that adrenaline has a late bronchoconstrictor effect. It seems doubtful whether these observations can be applied to the use of adrenaline and isoprenaline in human asthma. The former has been used for many years throughout the whole world and was often found to be the only substance that gave relief. No trace of a "boomerang effect" as expected by Hamburger and his co-workers is observed clinically, although naturally in chronic asthma the obstruction often returns when the adrenaline effect fades. In some cases "adrenaline resistance" is encountered: whether this phenomenon is related to that observed *by Hamburger is not known, and in the present state* of our [illegible] practical conclusions from an

[illegible]

This consideration must not prevent us from further investigation of the problem of adrenaline tolerance. From purely clinical experience I am certain that small (sub-optimal) doses of adrenaline or isoprenaline given at intervals of about 30 minutes have little or no effect. If, for instance, 5 minims are given half-hourly for 3 hours the effect may be nil, whereas 30 minims given at once will act dramatically. Also, if adrenaline is given once or twice per day, its effect usually remains unimpaired; if it is given frequently—every 2–3 hours—tolerance quickly develops. It seems possible that this development of tolerance is related to the fact that at some stage in the action

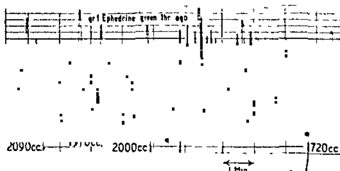


Fig 6.—Ephedrine effect

Male, aged 56 years moderately severe emphysema Vital capacity 1,700 cc One hour after ephedrine, 1 grain, had been given orally, the vital capacity increased to 2,020 cc Ephedrine, ½ grain and ¾ grain, did not show any effect

difficult to find. It varies between ⅛ grain and 4 grains. In children and adolescents it is usually ½–¾ grain, in adults ½–1½ grains, *but in emphysema and asthma of long standing the dose is often* higher. With such wide variation in the optimal dosage it is worth while to determine it spirographically. The vital capacity is recorded before and one hour after a test dose of ephedrine, and only if there is a definite increase in the vital capacity of at least 10 per cent can an ephedrine effect be assumed to be present (Fig. 6). It is not surprising to find that sometimes the patient reports subjective improvement although the vital capacity is unchanged. This is probably due to the central stimulating effect of the substance. If no spirometer is available, treatment should be started with a medium dosage of ½–¾ grain, and this dosage should be increased by ½ grain every few days until either a definite improvement or side symptoms occur. *In the latter case the dosage is at once reduced by ½–¼ grain.* If three daily doses are given, tolerance develops quickly—within 3–4 days (Herxheimer, 1946a). This does not happen if only two daily doses are given; this régime can be continued for long periods. The dose need not be increased if the asthmatic condition does not change in its degree. If it improves the dosage must be reduced, if it deteriorates the dose is increased. Sometimes an improvement announces itself by the fact that a dosage of ephedrine which has been well tolerated for a long time now causes unpleasant side-effects. The development of tolerance to ephedrine given in 3 daily doses finds its parallel in its action in the pharmacological experiment, where its effects decrease with each successive dose (Levinson and Essex, 1943).

The symptoms of overdosage (side symptoms) are many. Palpitations, trembling and irritability are the most frequent, but nausea and loss of appetite also occur from time to time. Rarer symptoms are drowsiness—in most patients the opposite occurs—dryness of the mouth, wide pupils with loss of accommodation for close work and, in males over 40 years of age, difficulties of micturition. The latter complaint may in fact be less rare than it appears, because the patients hardly ever relate it to the drug and usually mention it only if it is severe.

The optimal dosage often lies close to the dosage causing side

symptoms, sometimes so close that the drug cannot be used. In some of these, but not in all cases, a sedative given at the same time suppresses the side symptoms. Another means of [illegible] e (Meteph) [illegible] weight for [illegible] ubstance is marketed in tablets of ⅝ grain, and one tablet is approximately equivalent to ½ grain of ephedrine. Orthoxine (Curry *et al*, 1950) is another relative of ephedrine with similar effects.

Ephedrine is very widely used and many asthmatics make its acquaintance at an early stage. Their experience is of value and should be asked for when the history is taken If the answer is "it does not help" then usually too low a dosage has been tried, or it has been given in an acute attack, when it is useless. If the answer is "it does not agree with me", the dosage was obviously too great. If the answer is "it has helped some time ago but now it does not", it indicates that either tolerance has developed or that the asthma has [illegible]

[illegible] was not the relieving agent. Only if the relief was experienced after about 30 minutes or longer can a true ephedrine effect be assumed

Ephedrine can also be given by injection but this is rarely necessary. It is not clear why ephedrine given orally takes longer to act than any other substance. It behaves in this respect (and in others, such as the unpredictability of dosage and the side-effects) like the antihistamines. One might suspect that the substance [illegible]

[illegible] nistamines in enteric-coated capsules and found that several hours passed before any effects appeared.

Aminophylline, caffeine

Aminophylline is a very reliable anti-asthmatic remedy when it is given intravenously. Its effect is especially welcome when

given through a mask at the rate of 6 litres per minute. It is claimed that adrenaline-resistant cases respond to adrenaline after helium treatment.

The use of carbon dioxide inhalation has also been recommended (Tiefensee, 1929). I tried it many years ago (Herxheimer, 1932) and found that during the attack the increased ventilation caused by the carbon dioxide admixture to the inspired air was not tolerated by the patients. In the interval between attacks the stimulation by carbon dioxide may be used as a breathing exercise. A mixture of air with 2–4 per cent carbon dioxide regularizes the respiration and prevents excess loss of carbon dioxide in hyper-ventilation. It cannot be regarded as a major therapeutic measure in asthma. Carbon dioxide, however, has a powerful expectorant action (Basch, 1941). It can be used with great advantage in cases of asthma and emphysema when expectoration is made difficult by the viscosity of the mucus. If a mixture of 5% CO_2 and 95% O_2 is available in cylinders, this should be respired through a mask or a mouth-piece. Periods of 5 minutes are usually sufficient and may be repeated several times. If such cylinders are [illegible]

carbon dioxide cartridge of the type used for soda-water syphons. The bladder is mounted on a metal tube which can be opened and shut by a trigger and ends in a face mask. The patient holds the mask over his face, leaving ½–1 inch distance between the edge of the mask and the skin, and presses the trigger during 3 or 4 deep breaths. If he finds the carbon dioxide content of the inspired air too overwhelming, he should increase the [illegible] event him from [illegible] ave found this [illegible] use of oxygen by mask or by oxygen tent has been recommended for the severe asthmatic state. It may be useful in some cases, but it seems more important to open the obstructed air passages than to try to force oxygen through them. This will be useless in those which are completely obstructed.

the adrenaline-like substances have not brought sufficient relief or when a more lasting effect is required. It is rare that aminophylline is not tolerated if it is injected slowly. One ampoule (0·24 gramme)—in severe cases of asthmatic state double this amount—is required. Given orally, the effect is not as pronounced, but in many cases very helpful. I have found Monotheamine capsules (3–6 grains) useful. It is not effective in all patients, but it is remarkable that the 4 patients out of the series of 143 mentioned later, for whom no suitable antihistamine could be found, all responded well to Monotheamine. It has no central stimulating effect and can therefore be given at night or during the day. During the day it is useful as an alternative to ephedrine.

Suppositories of aminophylline (0·36 gramme) are more effective than oral capsules or tablets. The aerosol can also be useful; I have used it in 5 per cent and 10 per cent concentrations, especially in patients who had become too dependent on their isoprenaline inhalant and used it too often. For these an alternative inhalant not containing adrenaline or isoprenaline is desirable.

Trimethylxanthine (caffeine) and dimethylxanthine are substances which have been used in bronchial asthma. It may be that they act in the same way as aminophylline although they are not as effective. They are useful only in mild attacks. It is possible that the "cup of tea" which the asthma sufferer makes for himself during the night, acts because of its caffeine content or because of the local heat it supplies. But, of course, the effect may be purely psychological, as a cup of tea, at least in the British Isles, is expected to "do you good".

Helium and carbon dioxide

The use of helium for the symptomatic treatment of asthma has been recommended by Barach (1935; 1944). Its use is indicated in patients in whom respiration is continuously made difficult by hypersecretion. The mixture of 80 per cent helium and 20 per cent oxygen has a motility three times as great as ordinary air and will therefore penetrate capillary openings in partially blocked bronchi more easily. It is recommended to be

given through a mask at the rate of 6 litres per minute. It is claimed that adrenaline-resistant cases respond to adrenaline after helium treatment.

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The use of helium for the symptomatic treatment of asthma has been recommended by Barach (1935; 1944). Its use is indicated in patients in whom respiration is continuously made difficult by hypersecretion. The mixture of 80 per cent helium and 20 per cent oxygen has a motility three times as great as ordinary air and will therefore penetrate capillary openings in partially blocked bronchi more easily. It is recommended to be

given through a mask at the rate of 6 litres per minute. It is claimed that adrenaline-resistant cases respond to adrenaline after helium treatment.

The use of carbon dioxide inhalation has also been recommended (Tiefensee, 1929). I tried it many years ago (Herxheimer, 1932) and found that during the attack the increased ventilation caused by the carbon dioxide admixture to the inspired air was not tolerated by the patients. In the interval between attacks the stimulation by carbon dioxide may be used as a breathing exercise. A mixture of air with 2–4 per cent carbon dioxide regularizes the respiration and prevents excess loss of carbon dioxide in hyper-ventilation. It cannot be regarded as a major therapeutic measure in asthma. Carbon dioxide, however, has a powerful expectorant action (Basch, 1941). It can be used with great advantage in cases of asthma and emphysema when expectoration is made difficult by the viscosity of the mucus. If a mixture of 5% CO_2 and 95% O_2 is available in cylinders, this should be respired through a mask or a mouth-piece. Periods of 5 minutes are usually sufficient and may be repeated several times. If such cylinders are not available, I have used a carbon dioxide resuscitator. This little apparatus consists of a rubber bladder of about the size of a football which is filled to expansion by opening one small carbon dioxide cartridge of the type used for soda-water syphons. The bladder is mounted on a metal tube which can be opened and shut by a trigger and ends in a face mask. The patient holds the mask over his face, leaving ½–1 inch distance between the edge of the mask and the skin, and presses the trigger during 3 or 4 deep breaths. If he finds the carbon dioxide content of the inspired air too overwhelming, he should increase the distance of the mask from the face. This will prevent him from breathing too high a percentage of the gas. I have found this to work well in a great number of patients. The use of oxygen by mask or by oxygen tent has been recommended for the severe asthmatic state. It may be useful in some cases, but it seems more important to open the obstructed air passages than to try to force oxygen through them This will be useless in those which are completely obstructed.

Antihistamines

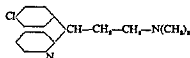
Treatment with antihistamines is even more difficult than with other drugs. The reason is that not only as with other substances must the dosages be increased with the severity of the bronchial obstruction, but there is also great individual variation in the reaction to these drugs. Antihistamine X may suit subject A perfectly, but may be toxic to subject B, whilst antihistamine Y may be toxic to both, but not to subject C. To give an example: A medical student was nauseated by 25 milligrams of Anthisan (an extremely small dose) but responded well to 25 milligrams of Phenergan. The same subject could take 550 milligrams (!) of Histantin with very little fatigue and only little improvement.

These great differences require that in every case substance and dosage should be tried out individually. This is perhaps the reason why some authors found the action of the antihistamines "disappointing". Dunlop and Hunter (1948) believe that they have no action at all, as in their experiments the controls improved more than the patients who received Anthisan. They gave rather small doses, however, and such trials are, in spite of their scientific appearance, of little value (*see* page 28) I do not find the antihistamines disappointing; they are excellent if they are used in the right dosage for the right patients. Their side-effects, which have been extensively described, are sometimes so unpleasant or incapacitating, that their use must be abandoned, as they cannot be counteracted. These effects, however, only make their use difficult, not impossible.

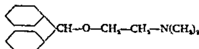
One very common side-effect of all antihistamines known to me is that they cause fatigue in at least some subjects. This fatiguing effect may be overwhelming, and it is often combined with an anti-asthmatic effect. But in some cases the anti-asthmatic effect is lacking, and in others it is present without fatigue. Because of this fatigue, the sedative effect of which is very desirable in most cases, it is advisable to use the antihistamines as night drugs only. If they are given during the day, the fatigue must be counteracted, for instance by amphetamine. Limitation to one dose in 24 hours has the further advantage

TABLE II

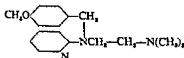
ANTIHISTAMINES



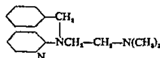
Chlortrimetone



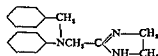
Diphenhydramine
(Benadryl)



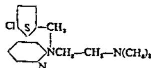
Mepyramine
(Neoantergan, Anthisan)



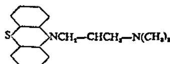
Tripelennamine
(Pyribenzamine)



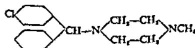
Antazoline
(Antistine)



Chlorothen
(Tagathen)



Promethazine
(Phenergan)



Chlorcyclizine
(Histantin)

Antihistamines

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is best taken together with food, and if nausea is present, it can be overcome by taking ½ grain of phenobarbitone together with the Anthisan before bedtime. The effect of the phenobarbitone appears before that of Anthisan and the patient is not awakened by the nausea. Given intravenously (25–50 milligrams) of Anthisan has an effect like Phenergan, but sometimes causes collapse-like effects, especially if it is injected too quickly.

(*iii*) *Benadryl* (diphenhydramine; Loew, 1947) has a general anti-asthmatic effect which is weaker than that of Phenergan and Anthisan, but it has a greater "drying" effect on the mucous membrane and it is therefore especially useful against rhinorrhoea. It does not act for longer than 6–7 hours. The dosage is 100–200 milligrams. Its side-effects, besides fatigue, are headaches, excitement and twitching of muscles. In those patients who do not tolerate Phenergan, Benadryl is surprisingly often effective.

(*iv*) *Histantin* (Chlorcyclizine) has an anti-asthmatic action which is weaker than that of Benadryl, but it acts for 12 hours and is therefore especially useful in vasomotor rhinitis. The dosage is 100–200 milligrams and fatigue is an almost regular side-effect.

(*v*) Of a number of other drugs my experience is not as extensive as of those named so far. They are pyribenzamine, chlorothen and Histadyl. They are effective in asthma in only a small percentage of patients and only if given in very large doses.

(*vi*) *Chlortrimeton* seems to be stronger and, weight for weight, approaches Phenergan in efficiency. Its action, however, seems to have a shorter duration.

(*vii*) *Antistine* (Antazoline) is weaker than all the other substances. Nevertheless, it can be useful in the very few patients who are intolerant to the stronger antihistamines.

In a number of cases it is impracticable to give the optimum anti-asthmatic dose of one single antihistamine as the side symptoms are too troublesome. In those cases the combination of two different antihistamines has proved useful. If nocturnal side symptoms are mild (the nausea which may follow Anthisan has already been mentioned) they can be suppressed by a small dose of phenobarbitone given simultaneously.

Procedure

My routine procedure in prescribing oral antihistamines in asthmatics is as follows:

(1) They are used *only in chronic asthma presenting* as a continuous mild asthmatic state or in mild or moderate nocturnal attacks recurring at frequent and fairly regular intervals, not in acute violent attacks.

(2) They are given only at bedtime or just before

(3) Phenergan is used first, usually in a dosage of 50–75 milligrams in an adult. If this dosage suppresses the nocturnal asthma and does not leave undue morning fatigue after 3 days, nothing more needs to be done. If there is morning fatigue and it remains intolerable, 2½–5 milligrams of amphetamine sulphate are given in the early morning to counteract it. Alternatively the dosage of Phenergan is reduced, if a smaller amount is sufficient to suppress the nocturnal attack. If the asthma is only partially suppressed and the sedative effect moderate the dosage is increased.

(4) If Phenergan causes sleeplessness or twitching of muscles, or if it is ineffective, it is replaced by Benadryl 100–150 milligrams. If this dose gives neither sleep nor suppression of the asthma, Anthisan 300–400 milligrams is tried.

(5) If 50–100 milligrams of Phenergan is effective, but causes too severe fatigue or side symptoms, a smaller dose (25–50 milligrams) is combined with 50–100 milligrams of Benadryl.

Results.—With this procedure the following results were obtained in 143 consecutive patients with moderate or mild nocturnal asthma which was only very mild (very severe cases were excluded): Phenergan alone was used in 98 cases (68 per cent). In 12 of these it was found that an appropriate amount of Anthisan—on the average five to seven times as much by weight—had the same effect. (This attempt to replace Phenergan by Anthisan was made only in a small number of cases.) Benadryl alone was used in 14 cases (10 per cent), Anthisan in 12 cases (8 per cent), Phenergan with Benadryl in 13 cases (9 per cent). Antistine and Histantin were effective in one case each. In 4 cases no effective antihistamine could be found. In all these cases except the last four, satisfactory improvement was achieved.

By "satisfactory" is meant that the influence of the asthma on the daily life of the patient decreased, and that it increased again when the remedy was omitted. The night which had been [illegible]

the diurnal asthma was not treated successfully, the general condition of the patient was improved by adequate rest during the night. Often, work could be resumed and invalidism avoided. Only in the minority of these cases could the antihistamine be omitted later. In most of them it had to be given for many months, or resumed after some interruption. The high proportion of favourable results recorded here is not surprising They are judged by clinical standards, and some psychological effects may have been included. On the other hand, different antihistamines were tried in many of the patients and only one or two were found effective. Also, the optimum dosage was used in every case, and the unsuitable diurnal type of asthma and very severe cases were excluded These factors acting together would naturally produce a higher proportion of successes than any single antihistamine given in sub-optimal dosage to unselected asthmatics. It is worth recalling that this result cannot be achieved by sedatives alone. In very mild asthma sedatives alone may sometimes achieve notable successes, but in cases of pronounced nocturnal asthma sedatives alone are almost useless. In this type the antihistamines are a very valuable therapeutic weapon They are so effective that the trouble taken in selecting the right substance and the right dosage will be well rewarded.

The parenteral use of antihistamines has not been studied extensively. If an antihistamine is injected intravenously, its action is, as would be expected, more powerful than when given orally. I have used Anthisan and Phenergan intravenously to interrupt severe asthmatic states. The use of these substances is not without risk, and I have taken the precaution of not giving it to patients who had shown themselves intolerant to the same drug when given orally. In addition, these substances were given very slowly, diluted in 10 millilitres of water or saline solution. Anthisan is given in amounts up to 50 milligrams but signs of

vasomotor collapse may occur, whereas this has not been observed after the same amount of Phenergan has been given. It is remarkable that their effect becomes noticeable only 10–15 minutes after injection. The sedative effect is strong, and the anti-asthmatic effect definite. If the vital capacity is taken, an increase can be noticed in most cases. An example of this is given in Fig. 7, Rubitsky *et al.* in 1949 have given pyribenzamine intravenously and have recorded the same experience. They claim that in the patient who has become adrenaline resistant the response to adrenaline is restored by intravenous injection of pyribenzamine. This observation can hardly be specific for any drug effect. It suggests that the asthmatic obstruction has diminished to such a degree that an ordinary amount of adrenaline becomes effective again.

asthmatic state, after adrenaline had failed.

I have, on many occasions, tried to use antihistamine aerosols. There is no doubt that they have a definite effect in experimental asthma. Rubitsky and his co-workers (1949) have shown this for histamine-induced and acetylcholine-induced asthma, and I have shown it in mild attacks of induced pollen asthma. One

weak that if quick relief is required this can be obtained much more efficiently by other means, namely isoprenaline or adrenaline aerosol.

No doubt we shall have more and possibly stronger antihistamines in the near future. Perhaps we shall one day have

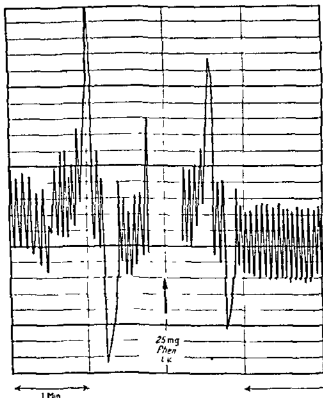


Fig. 7.—Effect of 25 milligrams of Phenergan given intravenously in a case of chronic asthma. The vital capacity before injection is 1,700 cc., 20 minutes afterwards it is 2,240 cc. (*By courtesy of the "British Medical Journal"*.)

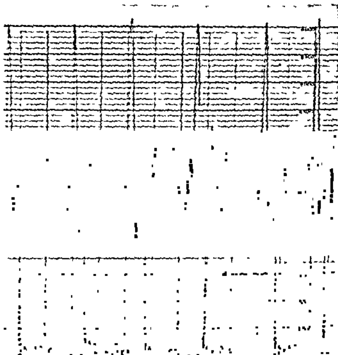


FIG 8.—IRREGULAR RESPIRATION IN ASTHMA

Male asthmatic, 31 years old, grass pollen asthma The tidal air between the various recordings of the vital capacity has no fixed level; the tidal air excursions vary considerably—between 500 and 1,500 cc.; and there is sometimes hyperventilation, for instance in the fifth minute

the ideal substance which neutralizes the asthmatic disposition of the bronchus without the side-effects which at present seem unavoidable.

Iodine

Iodine is an important drug, long established in the treatment of asthma. In all cases in which the typical viscid mucus is formed, blocking the smaller bronchi, the removal of the mucus [illegible]

not influence the amount present. In these cases iodine liquefies the mucus and permits its expectoration; very often it also seems to aid its absorption (Gordonoff, 1938). The relief that patients experience as soon as the mucus is removed is very considerable. Very often, the secretion becomes more fluid, or it disappears altogether; this may be a sign that absorption has been increased.

The amount of iodine required varies greatly I usually give ½ ounce of an 8 per cent solution of potassium iodide three times a day, but I have often had to give 15 per cent and even, in one case, 25 per cent. This amounts to 3·6–11 25 grammes (440–1687 grains) per day. As an alternative Lugol's iodine, 12–40 drops three times a day, can be given. The amount should be regulated according to its effect; usually the small amount of iodine contained in mixture of potassium iodide and stramonium is not sufficient.

Few patients show signs of intolerance or iodism. They complain of a "fresh cold"—a violently streaming nose—or show iodine acne. Such patients do not tolerate iodine, and even 1 grain per day causes unpleasant side-effects. One must also remember that asthmatics may become sensitive to iodine. A girl of 13 years of age, who had had two successful partial lobectomies for bronchiectasis, developed an asthmatic cough [illegible]

effects. Subsequently, she was found to be hypersensitive to

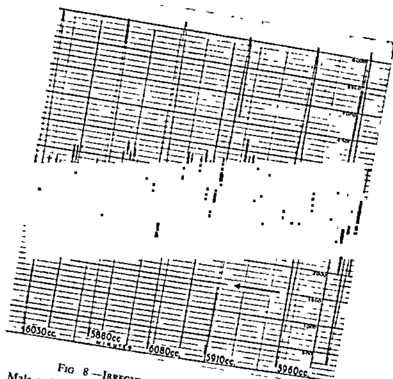


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Iodine

Iodine is an important drug, long established in the treatment of asthma. In all cases in which the typical viscid mucus is formed, blocking the smaller bronchi, the removal of the mucus is the first aim of treatment. Adrenaline or isoprenaline are often incapable of widening the air passages sufficiently to open them, and antihistamines may reduce the formation of mucus but will not influence the amount present. In these cases iodine liquefies the mucus and permits its expectoration; very often it also seems to aid its absorption (Gordonoff, 1938). The relief that patients experience as soon as the mucus is removed is very considerable. Very often, the secretion becomes more fluid, or it disappears altogether; this may be a sign that absorption has been increased.

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minute doses of potassium iodide. In none of my asthmatic patients has iodine ever provoked an acute attack.

The majority of patients require iodine for only 3 or 4 days Others need it continuously. This sometimes leads to the development of tolerance, and it is therefore advisable to give it for 3 or 4 consecutive days followed by a pause of 2–3 days.

I suspect that patients with a large amount of viscid mucus may be those who easily become "adrenaline resistant" as the mucus is neither moved nor diminished by adrenaline. In such cases bronchoscopic suction has been suggested by several authors (Waldbott, 1949). I agree with Pines (1950) that bronchoscopy is unnecessary in such cases if they are treated with the optimum amount of iodine. I have so far never been compelled to carry out this procedure in an asthmatic.

Sedatives

Morphine and codeine; barbiturates

Sedation is an important part of the treatment of asthma. The asthmatic patient is usually a "nervous" person, given to anxieties and worries. His respiration is more often than not irregular, and inclined towards hyperventilation (Fig. 8). This lack of stability is possibly one of the conditions for the development of asthma. It certainly favours the occurrence of attacks, as any hyperventilation will not only lead to excess loss of carbon dioxide, but also to an increased intake of airborne allergens. Hyperventilation may occur at the slightest stimulus and if an attack is feared or if it shows its first signs, hyperventilation is bound to increase the asthmatic condition and to worsen an attack which might otherwise subside. In all [illegible] factor is suspected a sedative should [illegible] the [illegible] ven [illegible] ent.
Phenobarbitone, $\frac{1}{4}$–$\frac{1}{2}$ grain, given two or three times daily, is usually sufficient. In some patients there is a cumulative effect and the amount must be reduced after a few days. If in an acute attack or in status asthmaticus quick and drastic sedation is

required, paraldehyde (15–20 millilitres) or ether (50–70 millilitres mixed with an equal amount of olive oil), given as a slow enema, can be recommended.

The use of morphine has been condemned by many because of its depressant action on respiration. It is doubtful whether this action and the depression of the cough reflex are its main disadvantages. Feldberg and Paton (1951) have shown that more histamine is produced under the influence of morphine, and asthmatics are particularly sensitive to this substance (Curry, 1946; Herxheimer, 1951). On the other hand, in some asthmatics—those who hyperventilate excessively—depression of the respiratory centre is desirable, and there are also a few patients in whom general sedation is difficult and morphine [illegible]

effect must be counteracted by giving adequate amounts of a sympatheticomimetic drug. "Adequate" means the amount of adrenaline or isoprenaline which is known to be effective in this patient. The dose of morphine should not exceed ⅙ grain when it is given for the first time.

Codeine phosphate is very useful in certain cases of asthmatic cough. As a rule this cough responds to ephedrine, antihistamine or iodine, but in a few cases the cough remains even if the hypersecretion has been stopped or expectoration is easy. If it appears in such cases that a persistent irritation in the throat is the cause, codeine is indicated, and only a large dose, 1 grain codeine phosphate, can be expected to be effective. It must not be given if expectoration is difficult and the bronchi are full of mucus.

Aspirin

Acetylsalicylic acid—aspirin—often has an action similar to [illegible]

I have observed that in some cases intolerance to ephedrine was removed by aspirin taken at the same time. In a number of cases

hypersensitivity to aspirin is present, and in these it may provoke severe attacks. It must therefore not be prescribed before the presence of hypersensitivity has been excluded.

Combinations of drugs

For many years asthma has been a happy playground for drug manufacturers. Knowing that one could not rely on one single substance, they combined several. Such tablets or powders often contain ephedrine, aminophylline and phenobarbitone or related substances, and sometimes others are thrown in, as caffeine or iodide. As overdosage must be avoided, each substance is represented by a small amount which, given alone, would be ineffective in most patients. Such combinations are sometimes praised by patients, and it is difficult to find the cause of their success. It may be that one of the constituent drugs has had a beneficial effect in a sensitive patient although its amount is too small to have an effect in many. As there are often three or more such drugs, the small chances for such an effect are, at least, trebled. In addition the well-known psychological effects may occur. Makers sometimes state that such substances potentiate one another when they are used in combination, but this has not so far been proved.

The main disadvantage of such drug combinations is that patients may require quite different optimum dosages of different drugs. If three substances are combined in a certain fixed proportion, the amount of one substance cannot be varied without varying the others, and one main aim of drug treatment in asthma, namely to achieve the maximum effect by those drugs to which the patient responds, cannot be achieved. This [illegible]

(*see* page 62). Different drugs may have to be used in the same patient for different purposes: an antihistamine to suppress attacks during the night, isoprenaline to abort attacks in the day, iodide to loosen expectoration, and possibly a general sedative. It would be convenient if one could combine all in one

preparation. As this is impossible, these substances must be prescribed separately This is a rather cumbersome procedure; but I cannot see how it is to be avoided.

If an antihistamine is to be given in daytime (for instance [illegible] to these drugs.

One word ought to be said here about cough mixtures. A large number of such combinations, old and new, exist. I do not want to discuss the voluminous literature on their expectorating effect (Gordonoff, 1938, Alstead, 1939, Basch, 1941, Boyd, 1946, and others); my personal experience is that in chronic cough caused by asthma very few of these combinations are effective besides those containing a sufficient percentage of potassium iodide. There is hardly any case in which the widely used Mist Ammon. et Ipecac. Co. (*N.F.*, 1949) has been known to

Ammonium bicarbonate	0·2
Tincture of ipecacuanha	0·6
Liquid extract of liquorice	0·6
Anise water	0·1
Camphor water	8·0
Water	to 15·0

diminish the cough There were a few which improved with Mist. Ammon. et Ipecac. Co. (*N.W F.*, 1947), sometimes called

Ammonium bicarbonate	0·2
Tincture of ipecacuanha	0·6
Camphorated tincture of opium	0·9
Liquid extract of liquorice	0·6
Water	to 15·0

"paregoric". Its beneficial effect is, perhaps, due to its very small content of opium which would act only in those patients who are extremely sensitive to it The Mist. Sod. Chlor. Co. (*N.F.*, 1949)—"hot Brompton mixture"—has more followers.

Sodium bicarbonate	0·18
Sodium chloride	0·6
Emulsion of chloroform	0·3
Anise water	*to* 15·0

I have not been able to elicit any plausible explanation of its action from my colleagues but I suspect that the heat conveyed by it to the pharynx and indirectly to the trachea and the main bronchi plays a great part in the relieving effect. This view is supported by the fact that hot packs applied to the neck will quickly relieve allergic oedema of the nasal mucosa (Dr. H. A. Lucas, personal communication). If heat is capable of doing this with the nasal mucosa, it may be similar with the mucosa of the lower air passages. Potassium iodide, ephedrine, the antihistamines and codeine are, in my experience, far more effective in relieving asthmatic cough than any of the cough *mixtures in common* use.

Aerosol combinations

The use of aerosols in asthma has proved to be efficient treatment, and the aerosols of isoprenaline, adrenaline, aminophylline and of the antihistamines have been mentioned in previous chapters.

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(1946) have written ...
practical application of a nebulizer it is important ...
aerosol should consist of droplets not larger than abo...

If this is the case, the aerosol seen at the ...
appears as a fine mist similar to cigarette ...
to rise in the air. Otherwise the cloud does ...
ous, and a part of the aerosol has do...

due to the weight of the larger droplets. Quick evaporation of the droplets must be prevented by the addition of glycerin or a similar substance.

The patient should be instructed how to use a nebulizer. As the depth of a single breath varies widely, no directions can be given as to the number of breaths to be taken. The patient should inhale until he notices a definite relieving effect. The number of inhalations must during 24 hours be varied according to the severity of the condition. Some patients tend to become dependent on their nebulizer so much that they almost become addicts. They inhale every half-hour or hour, and as this will soon lead to the development of tolerance, the number of inhalations in such cases must be restricted to the real requirements The patient should not inhale when he fears or suspects an attack, but when there are definite signs of it. (In some cases the use of a nebulizer leads to the development of a conditioned reflex: they experience relief immediately after using the instrument, long before the strongest broncho-dilator could have acted. If they are given an inert solution, this effect may last some days until the reflex is broken up.)

Aerosols have also been used in combination, and one of the most popular combinations has been that of atropine, adrenaline and papaverine Of these three components the amount of adrenaline is kept so small (0 2 per cent) that it cannot be expected to have much influence. I have used the other components (papaverine, 0 9 per cent and atropine, 0 2 per cent) separately in unpublished clinical trials The patients used these inhalants, without knowing their ingredients, for at least one week each and had to write down the result of every inhalation Their reports showed clearly that papaverine was the only substance which had a beneficial effect and I was able to substantiate this in spirometrically controlled experiments. It may be that the atropine exerts a drying influence on the mucosa, but it is impossible to discover this effect clinically.

The original preparation (Bronchovydrine) which was, at that time, the only efficient inhalant on the market, also contained "fresh adrenal medulla" and "fresh pituitary extract" thrown in for good measure. This preparation gained a wide

steps as in specific hyposensitization. The injections are given subcutaneously, and the concentration of the solution eventually raised to 5 per cent. Tuberculin has also been used for non-specific hyposensitization. The patient must not show any evidence of tuberculosis and the skin reaction to 0·1 millilitre of a 1:100,000 dilution, given intracutaneously, must be positive. If this fact is established, the course can be started with 0·1 millilitre of a 1:10-million dilution subcutaneously; this is increased in the usual way.

Whereas the injection methods do not permit a direct observation of the effect of the treatment, the inhalation method has the following advantages: the antigen is applied directly to the "shock organ", the bronchi, and the effect can be observed. The method is simple, but more complicated than the injection method. The patient is connected with a closed spirometer circuit which records the air exchange continuously and also permits the inhalation of an aerosol from a side-circuit (Fig. 9). From the change in the vital capacity the asthmogenic action of an inhalant can be deduced. If a very [illegible] the amount of inhalant can be moderately [illegible] increased to many times the original amount. If the attack becomes stronger, it can be aborted immediately by isoprenaline [illegible] same side circuit

[illegible] separately, and the subject should be urged to exhale and to inhale as fully as possible. When the subject is sufficiently trained and the recordings do not differ by more than 150 millilitres, the pressure pump connected with the spirometer by a side-circuit is switched on. The pump takes air from the main circuit and its pressure can be switched to one of a number of nebulizers. From here the air laden with aerosol returns into the inspiratory tube of the main circuit. Care must be taken that the same nebulizer and the same pressure is always used for the same subject; the time taken by the inhalation is measured

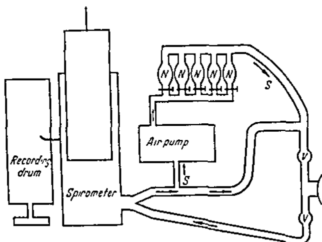


FIG 9—Aerosol-producing side-circuit attached to recording spirometer

V = Inspiratory and expiratory valves leading to and from the mouth-piece

S = Side-circuit attached to inspiratory tube leading from spirometer to subject

N = Nebulizers arranged between two manifolds Any of the nebulizers may be connected with the air pump by opening the clip below it

When the pump is switched on, it takes air from the spirometer, compresses it, aerolizes the liquid in the nebulizer, whose clip is open, and drives the aerosol into the inspiratory tube of the main circuit

(By courtesy of the "Journal of Physiology")

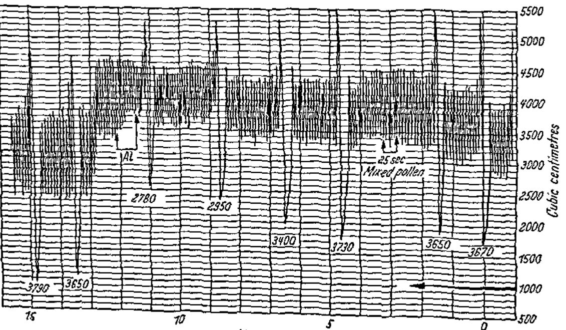


Fig 10 —Typical moderate attack of asthma induced by inhalation of mixed pollen extract aerosol for 25 seconds. The vital capacity before the attack is 3,660 cc One minute after the end of the inhalation it is still unchanged (3,730 cc) Two minutes later it has started to fall (3,400 cc) and it continues to fall. After the seventh minute it has reached 2,780 cc. and the attack is now terminated by the inhalation of 2 per cent isoprenaline aerosol (Al). It can be seen that the vital capacity returns promptly to its former value The sudden drop in the tidal air-level in the twelfth minute is caused by an adjustment of the spirometer drum (*By courtesy of the "International Archives of Allergy and Applied Immunology"*)

with a stop-watch. One minute after the end of the inhalation and then every 2 minutes the vital capacity is recorded again over a period of about 10 minutes. The desirable result is a very mild attack of asthma. This attack does not, as a rule, develop at once; the vital capacity 1 minute after exposure is unchanged; the next reading 3 minutes after the end of exposure may show a diminution by about 150–300 millilitres and then this decrease continues steadily. When the vital capacity has decreased by 400–700 millilitres, the attack is aborted by an aerosol of 1 per cent or 2 per cent isoprenaline into the circuit for 15–20 seconds. Within 1 minute it will be seen that the respiratory rate and the tidal volume increases. If the vital capacity is recorded again, it has reached or approached its previous value, and the attack is over. The tracing of such an attack is reproduced in Fig. 10. Five to seven days after this the next inhalation is given under the same conditions, but its duration is lengthened by 20–30 per cent, and this increase is continued in the same way. If the attacks become more severe the previous amount should be repeated and the next increase should be less than 20 per cent. If attacks are absent, the increase can be more rapid, but 40 per cent should not be exceeded. If the attack is milder than the one described, no change in the procedure should take place.

The severity of an attack is judged from the rapidity and the extent of the decrease in vital capacity. The time-lag the asthmatic effect appears is different in different subjects. Usually the first sign appears in the third minute. If in such persons it appears in the first minute, the attack is a little more severe than it ought to be. Other subjects experience the first effect after only 10–15 minutes, and in some cases no effect is apparent before 6–30 hours. The first decrease of vital capacity may only be by 150–300 millilitres and this is usually not noticed by the patient. Only when the vital capacity decreases by more than 15 per cent is a slight wheeze noticed Sometimes a cough at the peak of the inspiration or an itching feeling in the chest or between the shoulder blades is a premonitory symptom of the impending attack between the first and the third minute. As soon as it is clear that the attack is making the patient

uncomfortable, *iso*prenaline aerosol is released into the circuit for 10–15 seconds in order to abort it. The mildest attacks disappear spontaneously.

This method has many limitations and presents great difficulties. One of them is that it can be applied only to patients who can be trained to breathe with the spirometer and produce reliable tracings. Thus, for instance, it cannot be used for children under eight years old. Another, and much more important, limitation is that it must not be used in patients who have severe and continuous chronic asthma. In these patients the slightest error in the initial dose may lead to an acute deterioration of the condition and it may take weeks to overcome it. This leads to the main technical difficulty, namely that of finding the correct initial dose. As we know that overdosage causes hypersensitization it must be avoided at all costs. But how can it be avoided if patients vary widely in their sensitivity? The only way is to start with
any severe or moderate
result, to increase weekly
cent until the first attack
weekly increase is 20–40 per cent or less, depending on the severity of the attack. In Figs. 11 and 12 two different attacks are traced. The first was too severe. A very drastic reduction of the vital capacity was visible one minute after the inhalation and compelled immediate counteraction. An attack of this severity will with certainty lead to hypersensitization. The second tracing shows a very mild attack which is not apparent after 1 minute, but becomes just noticeable after 3 minutes. From then onwards it proceeds and gathers strength gradually but steadily until it must be aborted. Special attention must be paid to patients who do not show their reaction until 6 hours or later. If a new patient does not show any reaction during the first 30 minutes after exposure, it must not be assumed that his reaction is negative before 48 hours have elapsed. If a late reaction occurs, its degree is difficult to assess: if it is a mild and transient wheeze, it can be regarded as equivalent to an immediate very mild reaction. A wheeze lasting one day or longer may mean that hypersensitization has occurred and the next

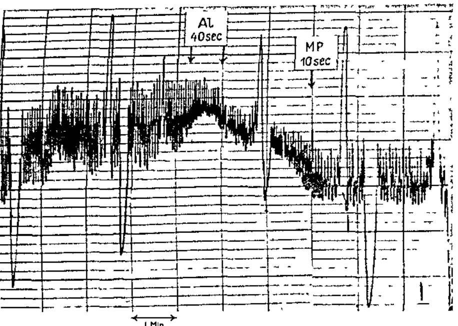


FIG 11 —Severe asthmatic attack induced by inadvertent overdosage of mixed pollen extract inhalation The inhalation of the aerosol ends at the arrow marked "MP 10 sec" Almost at once respiration becomes impaired This can be seen from the smaller tidal excursions At the same time the tidal air curve moves upwards, because expiration is more difficult than inspiration and air is retained in the chest which becomes inflated The vital capacity recorded 8 minutes later is reduced from 3,150 cc to 1,890 cc, and especially the reserve air is decreased, because expiration is hindered by the rapidly increasing bronchial obstruction At AI a 1 per cent isoprenaline aerosol is inhaled for 40 seconds The effect becomes visible towards the end of the 40 seconds, the tidal air increases sharply as the obstruction decreases and as the respiratory stimulus of the isoprenaline acts The vital capacity increases to 2,750 cc and 2 minutes later to 2,980 cc Most of the air retained in the chest during the attack has been expelled Attacks of such violence are likely to be followed by a state of hypersensitivity (*By courtesy of the "Lancet"*)

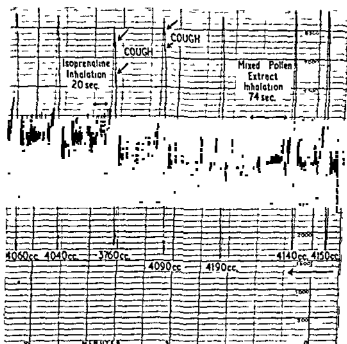


FIG 12 —VERY MILD ATTACK OF INDUCED ASTHMA

Male asthmatic, 25 years old, grass pollen asthma Vital capacity before attack 4,145 cc One and three minutes after the end of inhalation it is unchanged, but at the height of inspiration after the

dose must therefore be smaller than the one which provoked the reaction.

When a high dosage has been reached and a high degree of hyposensitivity achieved, boosting doses must be given in intervals of, perhaps, 8 weeks. During the whole course danger may arise from outside factors: a person believed to be only grass-pollen sensitive may also be mildly sensitive to dust, and exposed to dust at the same time as he is receiving a borderline dose of pollen extract intended to produce a mild attack. The result may be overdosage and hypersensitization; one must then go back to a very much smaller dosage and start all over again. This kind of setback becomes the more probable the more widespread the allergy of the patient is. Hypersensitization is almost bound to occur if the patient is continuously exposed to outside allergens of unknown quantity: This may be the reason why so many setbacks occur in polyvalent allergy with the injection method. There is no safe means of preventing such setbacks; many can be avoided if no attack is induced in doubtful circumstances, for example if the immediate previous history makes exposure to an allergen probable, or if there is a mild disorder of unknown origin, or if the vital capacity is reduced without such a disorder being apparent.

But in spite of all these difficulties and limitations it must be repeated that this method permits direct observation of the effect of the treatment and the testing of its result. It is therefore better than the injection method which does not permit of any observation. Only in a few cases can an effect be seen, usually many hours after the injection. We do not know for certain whether such a late reaction after injection of allergen always means overdosage and hypersensitization. Often it does; if with the inhalation treatment only a late reaction lasting more than 1 or 2 hours [illegible]e. It [illegible] fore [illegible] the result partially or totally and must therefore be avoided. Isoprenaline taken 3 or 4 hours before, ephedrine taken 8 hours before and Phenergan taken 18 hours before may protect completely and thus mask an attack (Herxheimer).

Attacks induced with mould extract seem, in the majority of cases, not to cause hypersensitization, and the attack does not increase in severity; on the contrary, it tends to recede after an initial asthmatic obstruction occurring immediately after the inhalation (Fig. 13). A graphic illustration of the various grades of severity of an induced attack is given in Fig. 14.

It is certain that more experience with the inhalation method is needed and that we are far from the possibility of its universal application. It is equally certain that it is one of our few reliable means of aetiological treatment, unfortunately yet restricted to a minority of cases.

Environmental factors and dietetics

Environmental factors are almost always implicated in the causation of asthma. If their causative action is proved, they should be excluded if possible. Such environmental factors may be seasonal, like pollen or mould spores, or perennial, like dust or feathers or animal emanations. Some perennial factors may appear as seasonal ones, if they are inhaled in large and asthmogenic doses only during certain seasons. Dust is such a factor, when it causes attacks only if inhaled in fog. In other cases two or more allergens are required to produce symptoms provoked by one of them. For instance, dust inhalation or tobacco inhalation may provoke an attack only during the grass-pollen season. If such factors are to be excluded from the environment they must be known, and in this respect the patient's history is of the greatest importance.

[illegible] prove [illegible] ling to give up dusting as there is nobody to take over her duties. It is worse when the asthma is caused by moulds in a damp dwelling and it is impossible to change it. If animal emanations or feather bedding are the cause, their removal should be easy enough, but, of course, good evidence for this aetiology is essential before radical changes are demanded. The fact that the asthma is mainly nocturnal is no reason to accuse the feather pillow. The skin reactions are not a reliable guide, and in cases of doubt the bronchial reaction should be investigated. In every

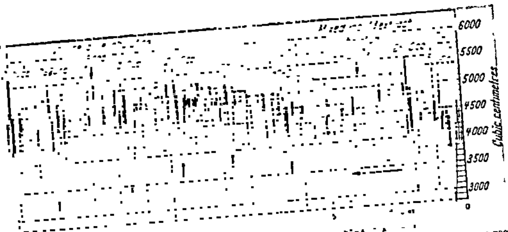


Fig 13 —Asthmatic attack [illegible] the vital capacity decreases from [illegible] cc to 1,780 cc and then rises steadily to 2,230 cc

Male asthmatic, age 39 years After 3 minutes' inhalation the vital capacity decreases from [illegible] cc to 1,780 cc and then rises steadily to 2,230 cc This attack would have subsided spontaneously within 6–10 minutes but was aborted by isoprenaline inhalation

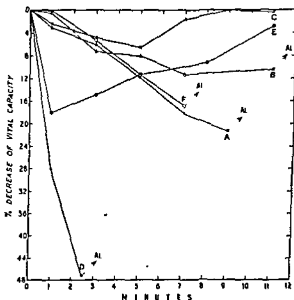


Fig 14—Decrease of vital capacity (in percentage of

decrease of the vital capacity in the first minute after the

case the intelligence and the co-operation of the patient should be enlisted in order to discover any causative factors in the environment, and it is advisable to let the patient detail all his usual daily or weekly activities. Occurrences like the use of face powder and the breathing of soap-sud fumes should not be forgotten. In spite of great care it will rarely be possible to detect all the factors, let alone to eliminate them. In the case of grass pollinosis, when there is only one single group of allergens, the aim can be achieved by removing the patient for this period into another climate without grass pollen; but this will often be impossible for economic reasons. Unfortunately, we usually have to deal with several factors; then their complete removal becomes impossible and we must be content with partial removal, which will lead to success only if the removed factor was a potent link in the combination.

It appears, then, that the elimination of environmental factors cannot usually be complete, and that this part of the treatment is often no more than a useful support for other measures It should not be neglected, however; our methods of treating asthma are so incomplete that every possible means to improvement must be utilized. I have often seen that when a housewife abstained from shaking out her mats she improved greatly, as only on these occasions did she inhale the overdose of dust to which she was not resistant. I also remember patients in whom the weekly visit to the cinema provoked attacks which were presumably caused by the clouds of dust, amply harboured in the plush seats, stirred up by the ever-changing visitors and inhaled by the excited and hyperventilating audience. Hospitalization often improves asthmatics without any other treatment, and they frequently relapse soon after discharge In such cases, an allergen may be the cause of the attacks, but psychological factors—removal from domestic friction, the feeling of safety under medical supervision—must also be considered.

Change of residence is often sought by asthmatics because they are convinced that it is "something in the house or the district". This may be true, but it is advisable that they should try the new district for some time before they make their final

decision. Holiday journeys often end in disaster. The long

patient returns home worse than he went. It is useful to warn *patients that if they become more wheezy on arrival, or the next* day, they should not wait and hope for improvement, but return home at once.

Dietary factors have often been accused as causes of asthma. There is no doubt that they exist, but in my experience they are rare. They very frequently cause allergic manifestations of the skin and of the gut, and the skin tests are often positive for many foodstuffs—eggs, milk, fish and pork being some of the main causes. If we ask the asthmatic patient whether these foods cause attacks, he will usually deny it, and there is no reason to disbelieve him: the skin reaction only shows that the patient is suffering from allergies in one or more organs, but it does not

to find attacks provoked by meals in general, whatever they [illegible] meals are concerned, and the larger

phragmatic movement, and the mild discomfort thus caused provokes the attack. Causes other than overloading of the stomach cannot be excluded; it might possibly be that the great loss of hydrogen ions by hydrochloric acid secretion into the [illegible] (similar to

For obvious reasons, heavy food and foodstuffs likely to cause flatulence should be avoided. The asthmatic with a long history is rarely well nourished and therefore needs plenty of food which should, as stated above, be supplied in as many

meals as possible. The obese asthmatic, who is much rarer, usually benefits from dietary restriction leading to loss of weight which will increase his mobility and sense of well-being. A decrease in the abdominal fat will also improve diaphragmatic mobility.

Special additions to the diet, for instance vitamins, meat extracts or calcium salts, have never been proved to be beneficial clinically; nor has their anti-asthmatic influence been proved experimentally. They are unnecessary, as are the "tonics" which patients so frequently expect.

CHAPTER VII

TREATMENT OF DISORDERS CLOSELY RELATED TO ASTHMA; COMPLICATIONS

Localized chest conditions

IF BRONCHIAL asthma is associated with pulmonary tuberculosis, both conditions must be treated concurrently. Severe asthma is rarely present with active and widespread tuberculosis, but more often asthma is associated with a fibrous tuberculous process of low activity. In widespread tuberculosis mild asthmatic obstruction occurs secondarily. It is possibly caused by the local bronchial inflammation and hypersecretion and requires anti-asthmatic measures.

Bronchiectasis and asthma are often associated. *In most cases* this bronchiectasis is a cylindrical widening of the bronchi in which the progress of the contrast medium is slowed down (di Rienzo, 1949); this type of bronchiectasis may be reversible (Waldbott *et al.*, 1950). Saccular or cystic bronchiectasis associated with asthma is rarer. The operative treatment of *bronchiectasis rarely improves the asthma.*

Atelectasis may occur in asthma as a result of continuous bronchial obstruction. It is caused by plugs of very tenacious mucus which may have to be removed by bronchial suction.

Intercurrent respiratory infections with fever commonly occur in chronic asthma. Often no new signs can be discovered by auscultation and radiology. There is usually an increase in bronchial secretion. The temperature subsides soon and the illness is termed "bronchitis". Whether this is correct, or whether there are small and radiologically invisible pneumonic foci, remains doubtful. The accompanying cough usually becomes worse for some time and often requires an expectorant. Penicillin injections are often useful, but before they are given, *allergic sensitivity to penicillin should be excluded.*

In other cases radiological examination reveals a focal

pneumonia which subsides very quickly. Physical signs are mostly absent as the extent of the consolidation is small. If treatment with antibiotics or sulphonamides is begun, the temperature subsides rapidly, but I have often seen this happen without any treatment. Nevertheless, the correct course is immediate therapy. It should be supported by bacteriological investigation of the organisms involved and of their sensitivity to antibiotics.

The question whether penicillin or similar substances should be given in order to treat the chronic inflammatory changes accompanying asthma should be considered for each patient individually. In my experience, no lasting improvement can be achieved in chronic asthma; the sputum becomes less purulent for a time, but soon after the treatment is omitted there is a relapse. The treatment should therefore be reserved for acute exacerbations and only if allergic penicillin sensitivity is absent. Aerosol treatment is rarely helpful if there is much secretion, the injection of high doses is preferable.

In congestive heart failure from extrapulmonary causes bronchial spasm sometimes develops, especially after febrile bronchial infections. In such cases ephedrine and isoprenaline are often badly tolerated, but very small doses of ephedrine (½ grain or less) are sometimes successful. In some cases of cardiac asthma bronchial spasm also develops, which is possibly secondary to pulmonary congestion. Here also small amounts of ephedrine are often helpful. It is possible that in some of these cases the bronchial obstruction is caused only by hypersecretion, and that muscular spasm is absent.

The treatment of emphysema and right heart failure is beyond the scope of this book. It is clear that when the emphysema is the cause of the failure, every attempt must be made to diminish the accompanying bronchial obstruction which increases the degree of emphysema. This obstruction is one of the primary causes of failure and, if it cannot be diminished, the failure is likely to increase. In the face of this powerful factor measures directed at the circulation and oxygenation can only have a transient success.

Chest pain is frequently encountered in asthma. Very often

its type suggests a pleural origin—the pain being felt only in the last part of the inspiratory phase. No effusion or pleural rub is found in most cases. This type of pain is nearly always associated with a persistent hard cough, and in most cases an effusion or pleural rub cannot be found. It must be assumed that cough alone can cause it, but, of course, a cough fracture and gross pleural involvement must be excluded. The pain subsides when expectoration has become easier and the cough has improved. Another type of chest pain in asthmatics is seen if the accompanying emphysema is pronounced and of recent onset. This pain is not of the pleural type; it is more a constant ache, and it may be caused by the altered shape of the chest. It responds well to mild analgesics, such as Compound Codeine Tablets (*N.F.*).

There are two conditions which are frequently seen together with asthma; arterial hypertension and peptic ulcer. Both are so common that their occurrence in combination with asthma is not surprising. Whether it is more than accidental, only accurate statistical analysis can show.

The treatment of asthma in cases of duodenal ulcer is not different from the routine treatment, and the treatment of the ulcer will hardly interfere with that of the asthma. In hypertension there may be some doubt whether adrenaline, ephedrine and isoprenaline are permissible. I have found that they are well tolerated. They are as necessary as in other asthmatics, in their optimum dosage, and I have not seen any ill effects. Naturally, isoprenaline is preferable because the pressor effect of adrenaline is absent.

Rhinitis

Allergic rhinitis or rhinopathy is the only allergic manifestation closely connected with asthma. Abundant presence of eosinophils in the nasal smear (Hansel, 1936; Mausman, 1945) will confirm the allergic character of the disorder. In some cases it is the forerunner of the asthma, and it may be present for many years before the first asthmatic symptoms appear. In many cases asthma and rhinitis start at the same time. Urbach and Gottlieb (1942) encountered allergic rhinopathy in 38 per cent

of 379 asthma cases (pollen asthma was excluded). They found that both are likely to have the same allergic cause if one disorder begins within 2 years of the other. They recommend that early specific treatment should be given at the first sign of rhinitis, in order to prevent the monovalent allergy from becoming polyvalent. At our state of knowledge it is difficult to support or to dispute this view. It is certain that there are many patients with rhinitis who never develop asthma. On the other hand, if rhinitis is the first sign of allergy, it must be taken as an indication that other manifestations may develop. Whether this can be prevented by specific treatment is doubtful. It has been stated that the suppression of the rhinitis symptoms by drug treatment causes the patient to expose himself more to the allergen and may thus induce asthma This statement can be regarded as a suspicion only; there is so far no evidence for it.

We know from many case-histories of patients undergoing courses of hyposensitization that shortly after successful termination of the course new symptoms appeared due to another allergen. Besides, the reactions of the nasal mucosa to allergens and to treatment are by no means always the same as those of the bronchi in the same patient. One can observe in some patients that asthma and rhinitis are caused by different allergens so that, at times, only asthma or only rhinitis is present. In many patients, of course, both occur at the same time. In such cases I have noticed that the nasal symptoms often precede the asthmatic symptoms by a period of from several hours to several days. The patient then usually reports his experience as a "fresh cold which later went down into the chest". In most of these cases it can be assumed that no fresh respiratory infection has taken place, because fever has been absent. The reason for the retarded appearance of the asthma may be manifold. (1) The patient may belong to the "late reactors" described elsewhere (page 68). This would not account for the appearance of the symptoms later than 12–36 hours after the onset. (2) It may be that the dose of allergen required to provoke asthma is bigger than the dose provoking rhinitis and a longer exposure must therefore occur before asthmatic symptoms appear. (3) The rhinitis may, by some unknown mechanism, promote the

its type suggests a pleural origin—the pain being felt only in the last part of the inspiratory phase. No effusion or pleural rub is found in most cases. This type of pain is nearly always associated with a persistent hard cough, and in most cases an effusion or pleural rub cannot be found. It must be assumed that cough alone can cause it, but, of course, a cough fracture and gross pleural involvement must be excluded. The pain subsides when expectoration has become easier and the cough has improved. Another type of chest pain in asthmatics is seen if the accompanying emphysema is pronounced and of recent onset. This pain is not of the pleural type; it is more a constant ache, and it may be caused by the altered shape of the chest. It responds well to mild analgesics, such as Compound Codeine Tablets (*N.F.*).

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FIG 15 —SIMULTANEOUSLY RECORDED THORACOGRAM (UPPER PART) AND SPIROGRAM (LOWER PART) ARTIFICIAL EMPHYSEMA

(Read from right to left)

From *A* to *B* expiration is obstructed by a screw clip on the expiratory tube leading from the subject to the spirometer Immediately after obstruction (at *A*) air is retained in the chest and the tidal air rises quickly to a new level The thoracogram shows a considerable increase in the chest circumference which occurs spontaneously When the obstruction is removed (at *B*), the excess air is expelled from the chest and the previous situation is restored The vital capacity taken at *C* shows the reserve air greatly increased Increase of chest circumference, reserve air and the upwards displacement of the tidal air-level all prove that during the period of obstruction the amount of air in the thorax was increased (*By courtesy of "Thorax"*)

CHAPTER VIII

PHYSIOTHERAPY

MANY authors recommend breathing exercises in asthma, but few have investigated the basic principles of such exercises experimentally. Before recommending them it must be decided what purpose such exercises should serve. Are they to be used during an asthmatic attack in order to diminish the obstruction, or should they make the respiratory action generally more efficient in the expectation that the patient would become less liable to attacks or could overcome them more easily?

The training of the respiratory apparatus in asthmatics aims at a higher ventilatory efficiency. A higher vital capacity and a higher maximum breathing capacity, or both, is therefore required. Most asthmatics who have long periods free from any obstruction have a very high vital capacity during these intervals; I have seen a number of cases in whom it was higher than in normal subjects. Their maximum breathing capacity is also normal, although it is not easy to verify this because hyperventilation is likely to cause asthmatic obstruction. It is easy to understand why asthmatics should have a high vital capacity. During their attacks they breathe against increased resistance: at first there is only the typical respiratory obstruction; but this leads to the retention of excess air in the chest, which creates further difficulties. One can imitate this situation by placing an obstruction into the expiratory pathway of a spirometer circuit. Almost at once air is retained in the chest, and the ordinary tidal inspiration very soon approaches the inspiratory maximum (Fig. 15). The same mechanism acts in the asthmatic attack. This can be observed if the movement of air is recorded continuously by the spirograph and the rib movements at the same time by a thoracograph. Fig. 16 shows such a tracing. It can be seen that air is retained in the chest when the attack starts, and at the same time the circumference of the chest increases as the ribs are lifted. As soon as an antispasmodic is given, the



Fig 15.—Simultaneously recorded thoracogram (upper part) and spirogram (lower part) artificial emphysema

(Read from right to left)

From *A* to *B* expiration is obstructed by a screw clip on the expiratory tube leading from the subject to the spirometer Immediately after obstruction (at *A*) air is retained in the chest and the tidal air rises quickly to a new level The thoracogram shows a considerable increase in the chest circumference which occurs spontaneously When the obstruction is removed (at *B*), the excess air is expelled from the chest and the previous situation is restored The vital capacity taken at *C* shows the reserve air greatly increased Increase of chest circumference reserve air and the upwards displacement of the tidal air-level all prove that during the period of obstruction the amount of air in the thorax was increased (*By courtesy of 'Thorax'*)

Minutes

FIG 16—SIMULTANEOUSLY RECORDED THORACOGRAM AND SPIROGRAM MILD ASTHMATIC ATTACK, [illegible] 22 years old, grass pollen asthma

mild attacks, however, it may appear feasible to improve the situation by increasing the volume of expiration, the inefficiency of which is the primary cause of the distress. There are, then, two groups of asthmatics who might benefit from breathing exercises—patients with chronic asthma suffering from chronic mild obstruction, and patients with mild acute attacks. Both groups will benefit if their expiratory range can be improved.

At this point, some experimental observations must be mentioned. Christie (1934) was the first to observe that some patients with emphysema could not exhale fully when they tried to do so from the point of maximum inspiration. They could, however, exhale quite fully if they started near the end of a normal expiration (at the respiratory *Mittellage*—mid-volume). He thought this phenomenon to be a sign of lung distension, characteristic of emphysema, and called it *distension phenomenon*. It is, however, not pronounced in all emphysematous patients (Hurtado *et al*, 1934; Kaltreider, Fray and Hyde, 1938). I have found that it occurs in many asthmatics, even during the free interval. In most cases it is not so pronounced that it makes full expiration impossible, but the expiration, when started from the point of maximum inspiration, cannot be driven as far as is possible when it is started from the *Mittellage* (Fig. 9 *a* and *b*, facing pages 20 and 21). The difference may vary from 200 millilitres to almost one litre. Observers experienced in spirometry therefore prefer to record maximum inspiration and expiration separately, or to begin with expiration if they intend to estimate the true vital capacity.

The reason for the phenomenon becomes a little clearer if the spirogram of such patients is examined. If exhalation starts from full inspiration, one observes that soon after the expiration has started, an obstruction becomes evident: the patient has to press with all his strength to drive out more air. This difficulty always arises before the expiratory tidal air level (*Mittellage*) is reached. If, however, he has inhaled to the maximum limit and then exhales in the normal way (instead of trying to exhale maximally), the expiratory movement from full inspiration to the mid-volume is carried out without any apparent difficulty and without any exertion; yet it does not reach the *Mittellage*

at once but in steps of several inspirations and expirations (Fig. 4 *a* and *b*). These, taken together, require more time than one forced expiration to the mid-volume. In both cases expiration to the mid-volume takes a longer time than in the normal subject. This shows that full inspiration causes resistance to expiration whether the latter is forced by will power or whether it is left to the natural forces (the elasticity of the lung and the weight of the thorax). If expiration is forced, the resistance encountered is even greater than otherwise.

Full inspiration is therefore an important cause when expiratory obstruction arises suddenly, but is not the only one The following experiment will show this. When a patient, after maximum inspiration, exhales normally and has reached the tidal air range but not yet the mid-volume (Fig. 4*a*, c), he is asked to exhale fully and forcibly. It can now be seen that heavy resistance arises at once; not only is expiration slowed, but one can hear a wheezing sound from the very moment at which expiratory force begins to be applied by the patient. This wheeze continues during the whole expiration. It means that the lumina of some air passages have at this moment become much narrower. We must therefore assume that the expiratory obstruction already present has been increased by the expiratory pressure. This muscular factor will act the less, the nearer to the mid-volume that forced expiration is started. Rahn and his colleagues (1946) found that the maximum expiratory pressure could be increased by increasing the volume of air in the lungs. Mills (1950) has also shown that, with a full chest, contraction of the thoracic muscles is more effective than with a low chest volume. It appears, therefore, that the possible expiratory pressure will be smaller near the mid-volume, and that the inability of the patient to produce a high expiratory pressure at that point, together with the absence of a preceding maximum inspiration, is the reason that he can exhale much more deeply.

It must be assumed that resistance to expiration arises in the bronchi and that it is caused by a decrease in their lumina, in some cases by their complete closure. The suddenness of the phenomenon rules out swelling of the mucous lining or hyper secretion as the cause. It can only be muscular contracti

A substantial narrowing of the bronchial lumen in expiration also occurs in the normal subject, as Ellis (1938) and di Rienzo (1949) show. It is not caused mechanically by the increase in intrathoracic pressure, as the oesophagus does not change its lumen. It is, however, dependent on an intact thoracic cage and intact nerve supply. We are therefore forced to the conclusion that this bronchial constriction is an active muscular process which is reflexly connected with the point of maximum distension and the whole of the expiration. In normal subjects the constriction does not hinder the expiratory air stream and no difficulty is created by exerting high expiratory pressure. In asthmatics, however, the difficulty does arise and the bronchi almost close up. It is known that the bronchi in asthmatics are abnormally excitable (Hurst, 1943). The conclusion is therefore drawn that the increased bronchial excitability in asthmatics is the reason why maximum inspiration and high expiratory pressure cause immediate spasmodic contraction. Its obstructive effect is enhanced if oedema or hypersecretion are present.

The import of our considerations for the practice of breathing exercises is evident As full expiration must be trained—full inspiration being easy and unhindered—it must be trained so that the asthmatic obstruction is as small as possible and not so that it is increased. Expiration should therefore never start from the full inspiratory position or near it. It should start at the [illegible] at the end of normal

[illegible] the chance of keeping the bronchi open.

Hofbauer (1921), guided by his great practical experience, advised that expiration should be accompanied by humming. This device ensures that the expiration proceeds as slowly as possible and as far as possible. Livingstone and Gillespie (1935) used a similar technique. It has the advantage of [illegible] hyperventilation which, as I have shown (Her[illegible]ner, 194[illegible] leads to loss of carbon dioxide and cause[illegible] asthmatic attacks.

We must now consider [illegible]

used to assist breathing exercises. A number of older appliances —the breathing chairs of Rossbach and of Strumpell, the breathing belt of Quincke—were intended to support expiration by compressing the abdomen or the lower part of the thorax, but they have not found general application. Christie (1933) advocated an abdominal belt, Warner and Doidge (1939) a costal belt. I have investigated the influence of these belts by means of the spirometer, by the thoracograph and radiologically (Herxheimer, 1948b; 1949a) The abdominal belt keeps the diaphragm on a higher level in the normal and in the emphysematous subject, and there is little reduction in the vital capacity. The latter is probably due to the fact that the ribs are lifted and remain in this new position during normal quiet respiration while the belt is worn. In full inspiration the ribs can be lifted higher than without the belt—apparently the ribs can be lifted more easily with the support of a diaphragm fixed at a high level. This will lead to a shift of ventilation within different parts of the lung and is, perhaps, a reason why some emphysematous patients find that the abdominal pressure is beneficial.

The action of the costal belt is different; it prevents the ribs from being lifted to their abnormally high inspiratory position, and it forces the diaphragm to a lower level. The vital capacity is always reduced, because the limitation of the rib movement can only be compensated in part by the lowering of the diaphragm. In emphysematous patients the latter has often already reached its lowest possible level and cannot be lowered any further by the influence of the costal belt. I have, however, found the costal belt useful in those asthmatic patients who, under the influence of frequent attacks, have adopted the habit of

increases after a few days' training with the belt. It must, however, be remembered that in emphysematous patients there are

limits to the diaphragmatic activity, since fibrous atrophy of the diaphragm frequently occurs (Fromme, 1916).

There is another aspect of breathing exercises in asthma which ought perhaps to be mentioned. This is their psychological influence. The asthmatic patient often requires strengthening of his self-confidence. If the physiotherapist can convince him that by following his instructions he can ward off attacks or make them less severe, and if attention to the technique occupies his mind, a definite success can be expected in a patient in whom anxiety is an aggravating factor.

Conclusions

The following conclusions can be drawn from these considerations:

(1) Breathing exercises are useful only for certain groups of asthmatics. These are the patients with continuous mild asthma and those with acute mild attacks. The latter should carry out exercises during the attack. In the free intervals exercises are useless except for the learning of the technique.

(2) The purpose of the exercises is to train slow full expiration with the least possible expiratory pressure. This precludes full inspiration and requires full enlistment of the abdominal muscles, diaphragm and lower ribs.

(3) Hyperventilation must be avoided.

(4) An abdominal belt may be useful in some emphysematous patients for altering the pattern of lung ventilation.

(5) A costal belt is useful in those asthmatic patients for whom exclusively costal breathing has become a habit without being a necessity.

(6) The psychological influence of breathing exercises in asthmatics is valuable.

CHAPTER IX

PSYCHOLOGICAL TREATMENT

ASTHMA is one of the disorders termed psychosomatic. Although we do not know whether psychological factors can cause asthma without an allergic background, it is certain that they may act as strong contributory factors and thus provoke an attack or maintain it. This influence of the nervous system may become effective in various ways. Respiration may become excessive or irregular, the circulation in the respiratory organs may be changed, or there may be direct nervous impulses through the parasympathetic or sympathetic pathways to the bronchial musculature or the mucous membrane. Psychological triggers, such as excitement, prolonged anxiety or worry, may fire off such impulses from the cerebral cortex. Sometimes associations of former attacks (conditioned reflexes) may play a part. In other cases an unsatisfactory social or sexual situation may unconsciously provoke an attack by mechanisms which are unknown.

In the latter cases treatment by an experienced psychotherapist will be required. In many others the physician can contribute much to the psychological treatment. The fact that so many probably quite indifferent remedies have proved valuable in the hands of those who first described ("discovered") them and were enthusiastic in their evaluation in itself shows the value of psychotherapy. The asthmatic attack can, in a number of subjects, be avoided, or at least kept in check, by the confidence of the patient that it can be overcome. Confidence is what the patient requires, and if the doctor can inspire it an essential part of the treatment has been given. This is especially important in children; numerous examples can be given for the fact that an increase in self-confidence diminishes the number and violence of attacks. The opposite is also true. In children, for instance, the introduction of isoprenaline with its instantaneous action often causes a considerable change. The attacks,

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which can easily be cut off within a few hours, sometimes minutes, become rarer and eventually disappear altogether. In such cases, naturally, the anxiety of the parents has been allayed as much as that of the child. In other cases I have induced short attacks with histamine or acetylcholine and aborted them after one or two minutes. The quick removal of the attack impresses older children and removes much of the previous apprehension and fear. In such cases, usually adolescents, the whole attitude to the asthma changed, and as the anxiety factor disappeared, the other factors were not strong enough to cause more than transient and negligible attacks. On the other hand, it is well known that when a nebulizer is forgotten or broken, this alone can provoke an attack within a short time, because its presence is an important constituent of the patient's confidence.

It is clear that in these circumstances one of the main tasks of the physician must be to strengthen the confidence of the patient. It must be impressed on him that one of the reasons for his attack is his own anxiety and concern and that he must not succumb to it, that by contempt for the attack and by diverting his attention he can do much to decrease its intensity. The asthmatic is usually more intelligent than the average patient, and it is often possible to convince him and to obtain his co-operation. This is more difficult with the parents of asthmatic children who often cannot be persuaded to conceal their anxiety carefully. The child, sensing this anxiety, naturally loses all confidence when he sees that his parents are frightened. If parents are too stupid or uncooperative, it is advisable to separate the child from them and, if possible, transfer it to a boarding school.

In those patients in whom continuous worry plays a part, it will sometimes be possible to prevent its excessive influence. A number of patients will gradually learn by self-observation how often psychological influences are at work and this insight is the first step in minimizing their effect. There are, of course, many reasons for worry and excitement which cannot be eliminated. Constant friction in the family, increased possibly by overcrowding or sexual maladjustment, are conditions which

cannot be altered by the physician and often not by the psychotherapist. Sometimes the almoner is more successful in improving the patient's environment.

If the physician wants to increase the self-confidence of the patient, he must first win his confidence. He must listen with patience to his history and show him the sympathy he deserves. Experience will teach him that everything the asthmatic reports may be of importance, although much of it is inaccurate or based on wrong observations and can be disregarded. Many patients, for instance, accuse the "change of weather" as one of the causes of their attacks, but observation soon shows that they accuse this factor only if an attack occurs, and that abrupt changes of weather frequently fail to cause attacks. Experience will also teach the physician to take the greatest possible advantage of previous attempts at treatment: if a patient says that he could not tolerate ephedrine tablets, this is a good reason for giving this drug in very small dosage if at all. If he reports that they helped at one time but not recently, this points to a possible success with increased dosage.

Only prolonged observation can show how much improvement can be achieved and it would be wrong to try to win the confidence of the patient by promising him a cure. There is no definite cure for asthma, at present, but in many cases it is possible to improve the condition so much that the patient can manage himself. If the patient wants to know his prognosis, he should be told that there are good prospects of his improvement, but that it will take time for the correct method of treatment and the individual dosage to be found. This cautious prognosis is usually received well; it prevents disappointment if progress is slow at the beginning.

Physicians who regard asthmatics as psychological weaklings or as hysterical should leave the treatment to others. They should not forget that asthmatics with strong psychological factors may die in an asthmatic attack just as well as patients suffering from allergic asthma.

CHAPTER X

PRACTICAL PROCEDURE

THIS chapter describes some details of procedure which have not been previously dealt with. It will also give a few typical examples of treatment.

History-taking

The following special questions should be included in the history:

(1) Asthma or other allergic disorder in the family?
(2) How long has asthma been present?
(3) Since when have associated allergic disorders been present?
(4) What is known about the circumstances of the first attack?
(5) Is there any seasonal periodicity, or any other environmental cause?
(6) How often do attacks occur? How long does the acute stage last? How long the after-effect? Do they occur more during the day or more during the night? Are the intervals between attacks completely free of wheeze?
(7) Does worry or other excitement cause asthma?
(8) Is there breathlessness on exertion apart from the attacks? Is cough often present or only after attacks? Is the phlegm easily got rid of?
(9) Occupation? Tobacco?
(10) What has been taken or done against the asthma? Tablets? Inhalations? Exercises? With what success?

Examination

Routine examination of the whole body should be carried out. Special attention should be paid to deformity of the chest, hyper-resonance, an area of heart dullness, the presence of rhonchi (if absent with normal respiration, whether they are present on forced expiration).

Special investigations

If the diagnosis of asthma is in doubt a histamine test (*see* page 8) should be carried out

If the possibility of localized chest disease is present, a radiograph of the chest should be taken in every case if a recent picture is not available.

If the history shows definite evidence of polyvalent allergy of the bronchi, skin tests are not required, since their value as circumstantial evidence would be much smaller than that of the history.

If the history makes polyvalent allergy possible or probable, skin testing should be carried out, preferably by prick tests with concentrated extract. If the skin test shows only one or two allergens as positive, these substances and those which are incriminated by the history should be tested also by the inhalation method, provided that the asthma is not severe.

If the history incriminates only one or two allergens, skin tests should be carried out and, in every case, inhalation tests should be attempted, provided that the asthma is not severe.

If a nasal condition is present the allergic character of which is doubtful, a nasal smear should be made and an ear-nose-throat specialist consulted.

If ingestants are suspected in the cause of the disorder, the foodstuffs in question should be eliminated from the diet for one week; if the asthma disappears during this period, they should be added again in order to test their action. If there are a number of incriminated ingestants, a diet consisting of fruit and vegetables should be instituted for four days. If it does not provoke asthma, other parts of a normal diet should be added successively at three-day intervals: butter, sugar; bread; cream, milk; potatoes; beef, veal; animal fats; mutton, pork; fish. Weak tea and fruit juices may be added at any stage. If, at a certain point, asthma reappears, the diet factor most recently introduced should be omitted again until the asthma has disappeared and then added again. If the asthma returns a second time, this factor should be eliminated for good and the remaining factors tried.

If drug sensitivity is suspected, skin and inhalation tests should be carried out whenever possible.

An examination of the blood for eosinophils is usually not necessary.

Case reports

Every case must be treated differently. Some examples are given:

Case I.—Girl of 7 years Attacks every 4–8 weeks, lasting from 6 hours to 2 days, with 3–5 days of after-effects; sometimes after excitement; all the year round. No allergy detected.

Advice· Symptomatically isoprenaline tablets sublingually: in case of an attack, 10 milligrams every 3–4 minutes until relief is felt. In case of palpitations, removal of tablets from mouth. In the after-period ½ grain ephedrine on waking and at midday. (*Note*. The ephedrine dosage may need adjustment.) Parents must not show anxiety. If they cannot avoid showing it, removal of child from home environment to be attempted. If symptomatic medication does not succeed, evaluation of drug effect by spirometry. So long as the attacks remain as rare as they are now, there is no need for continuous ephedrine or antihistamine treatment.

Case ii.—Boy of 11 years. Asthma since early childhood, continuous for the last 5 years, worst in summer. Wakes once or twice every night with a wheeze, and has to use spray Has lost much schooling, but plays games after a fashion, although running makes the wheeze worse Examination shows a small "skinny" child considerably under weight Chest is deformed with protruding sternum, round back. There are massed inspiratory and expiratory rhonchi. Skin tests are positive for various kinds of pollen, house dust, animal hairs.

Comment: Such severe cases of asthma with emphysema can often be much improved, as the treatment is carried out at a time when there is a strong natural tendency to improvement. An antihistamine at night will, in all probability, prevent the night attacks. Such children commonly need large doses. I suggest to start with Phenergan, 50 milligrams at bedtime, warning the parents that the child may be tired in the morning. If the nights become better, but are still broken, increase to 75 milligrams or even 100 milligrams. If they do not improve,

after 3–4 days' trial, amphetamine sulphate, 5 milligrams, should be given on waking.

Case iv.—Man of 33 years, moderate asthma for many years, without seasonal variations. During winter often bouts of "bronchitis". These start with a temperature of up to 102 degrees. Subsequently the cough becomes more pronounced and an acute attack develops which may last many days. At [illegible]

ephedrine, but "they" have lost their effect. The doctor has given him an injection of adrenaline, but this has given only a little relief.

Comment: This is a case of chronic asthma with little or no hypersecretion at ordinary times. When, as at present, infection intervenes and viscous secretion develops and dominates the picture, potassium iodide, 3 grammes (45 grains), given in 3 [illegible] expectoration will [illegible]

sary to increase the amount of potassium iodide if liquefaction of the sputum is not sufficient with the dose mentioned. It should not be given for more than 4 consecutive days, as tolerance develops quickly. In the few patients who are hypersensitive [illegible] be reduced drastically. If iodism is [illegible]

facilitate expectoration as much as possible. Isoprenaline inhalant may also help.

Case v.—Man of 44 years. Has been in an asthmatic state for 5 days. Sits up in bed in extreme dyspnoea. Asthma has been present for 8 years, during the last 2 years continuously. Has been giving himself injections of adrenaline, 8 minims once or twice a day. Recently he has given himself up to 10 injections in 24 hours. Cannot sleep; there is hardly any cough, and wheezing is audible from a distance.

Comment: It is likely that the frequently repeated injections of adrenaline have made the patient tolerant to even large amounts of this substance and also of isoprenaline. Aminophylline, 0·25 gramme intravenously, should be tried and injected slowly. If a beneficial effect is present but not marked,

unknown to the patient. The recording of the vital capacity is a simple and not over-sensitive method of measuring the degree of bronchial obstruction. The aerosol-induced asthmatic attack can be successfully used to test the asthmogenic effect of allergens and other substances as well as the protective or curative effect of therapeutic measures. The patients selected for such assessment must be in a stable asthmatic condition whose small variations are known and slow in developing. Clinical observations on such patients may give a satisfactory result only if an objective guide—for instance the number of relieving inhalations required during a given period—can be found and if a number of different remedies is tried successively in the same patient.

(6) Theoretically the most promising treatment is elimination of the allergizing factor either by its removal or by hyposensitization. For many years the latter has been carried out by injection of increasing doses of allergen, but the degree of its success has never been assessed objectively. Bronchial hyposensitization by aerosol inhalation offers the possibility of objective assessment. It has proved effective in a number of cases, but the method requires further study and simplification before it can be used generally.

(7) In symptomatic treatment the most reliable drugs are the sympathicomimetic amines, adrenaline and isoprenaline. They act quickly and strongly against any kind of bronchial obstruction, but their effect lasts only for a few hours. Their dosage must be determined in each case not only individually, but also according to the violence of the obstruction.

(8) Ephedrine and the antihistamines have a weaker but more sustained action which, in the latter, may last longer than 12 hours. It may be that they are more effective in reducing mucosal oedema than bronchial spasm. Their use is made difficult by the wide range in dosage and in individual response. They are useless against violent acute attacks, but most useful in moderate chronic asthma; the antihistamines are also useful, if given intravenously, in the severe asthmatic state. The combination of an antihistamine with sedative side-effect for the night, and of ephedrine for the day has proved very effective in chronic asthma.

CHAPTER XI

SUMMARY

(1) *Bronchial asthma should be defined as bronchial obstruction caused by transient changes in the bronchial wall.*

(2) This obstruction may be caused by muscular constriction, mucosal oedema, hypersecretion, or a combination of any of these factors.

(3) There are many types of asthma: mild and severe, nocturnal and diurnal, continuous and periodic asthma can be distinguished for the purpose of treatment. It would be preferable to have an aetiological classification, as various aetiological factors are known: allergic, psychological, irritative and biochemical. But usually these do not occur alone; they occur in many combinations of different proportions. Moreover, the mechanism by which they cause bronchial obstruction is not known. *Therefore, an aetiological classification cannot be* attempted. The only therapeutic benefit derived from our knowledge of aetiology is that it may be used to counteract those aetiological factors known to be acting in a given case. The same holds good for the known anatomical causes of asthmatic obstruction: Muscular spasm, mucosal oedema and hypersecretion which may occur singly or together.

(4) Treatment can be carried out in three different ways: (a) by counteracting known aetiological factors, (b) by counteracting symptoms, and (c) by methods the *rationale of which is* unknown.

(5) A high percentage of beneficial, if temporary, therapeutic results must be expected in asthma with every treatment from which the patient expects improvement. The relative values of these treatments can therefore not be assessed by clinical impressions or by the common control methods. Special control methods must be used. These include the recording of objective signs of increasing or decreasing bronchial obstruction occurring not immediately after treatment but after a *definite latent period*

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(9) Aminophylline given intravenously may replace adrenaline or isoprenaline in the acute attack and is also effective in the severe asthmatic state. Some effect can also be obtained by its rectal or oral administration.

(10) Sedatives are indispensable in asthma, and elimination of the contributory psychological factors must be attempted whenever possible.

(11) Iodine is the most potent drug against bronchial obstruction which is caused by viscid hypersecretion.

(12) Breathing exercises should be used in cases in which the co-ordination of the breathing movements is permanently deranged. Hyperventilation and deep inspiration must be avoided. The psychological effect of breathing exercises is beneficial.

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